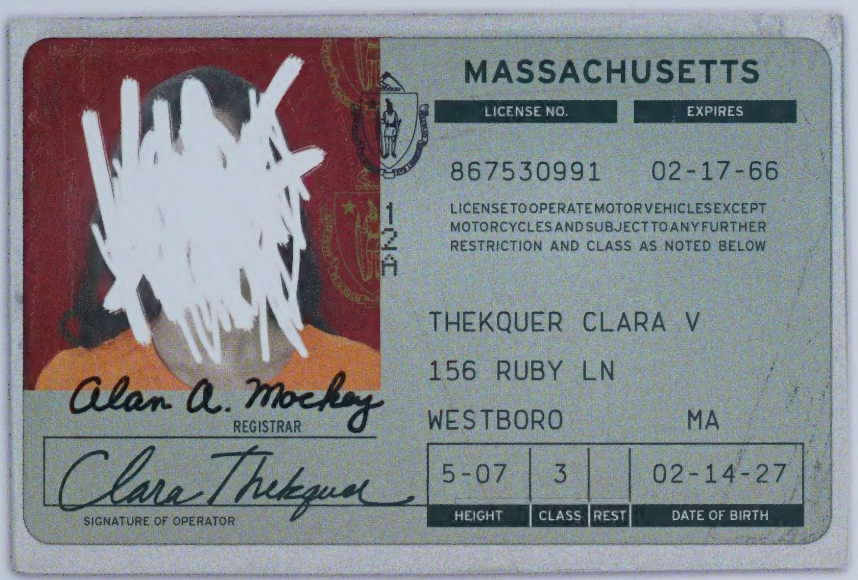
HARVARD
medicine
SPRING 2019



Mental health disorders have long been misunderstood and stigmatized. Now, research is leading to treatments and knowledge that is helping to dispel myths and misconceptions.

a sense of place

The annual McArthur Cup hockey tournament was held in late March. Begun by Harvard Business School and named after former HBS Dean John McArthur, the tournament is open to club teams from business and other professional schools in the Boston area and Canada. This year, the Harvard Med/Law team that defended the sheaves-and-rampant-lion shield included two HMS students, fourth-year Josephine (Josie) Fisher (dark jersey, left of center), and second-year Michael Seward (dark jersey, right of center).

Extramural hockey has been a pastime of HMS students for decades. The Class of 1958 was particularly avid. Class members who periodically faced off against med school teams from Tufts University and Boston University included Calvin Collins, William Elkins, Anthony Patton, and Rodman Starke, joined by James Fife, MD '55. Patton, while on Harvard College's hockey team, played in the first Beanpot, an on-ice rivalry begun in 1952 between Boston College, BU, Harvard, and Northeastern University.

STEVE LIPOFSKY

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INCLUSIVE VISION: Research and programs addressing mental health care and the causes of mental illness are active across the HMS community. Edith Gahleitner, an HMS graduate student shown here at the Tozzer Library at Harvard University, plans to investigate the intersection of psychiatry and child protection issues.

COVER: MATIAS PALUDI

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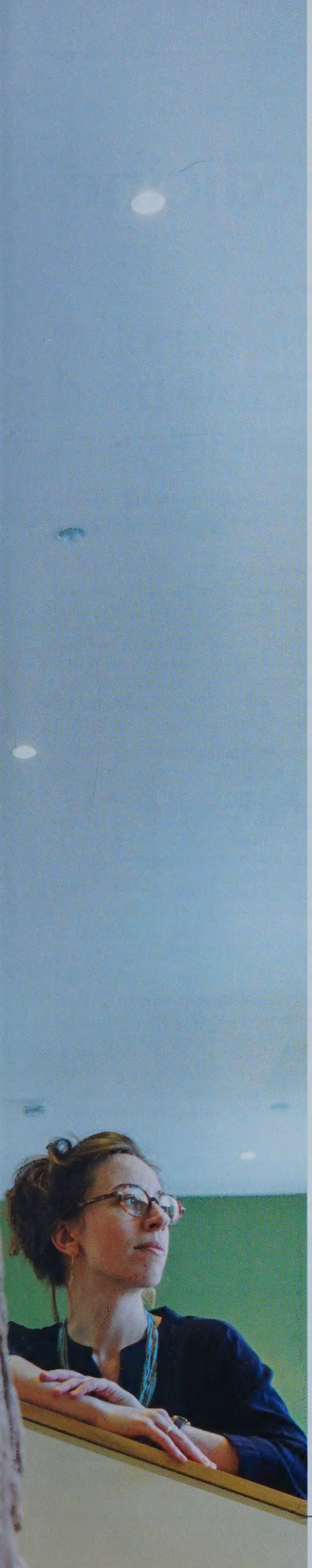

JOHN SOARES

SPECIAL REPORT
MENTAL HEALTH

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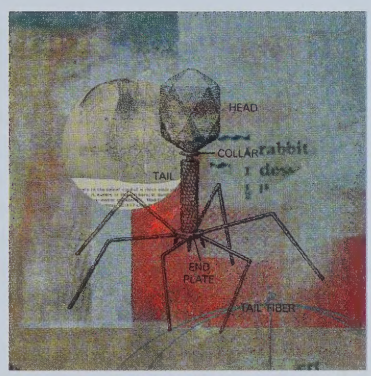

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A Complex Problem that Touches Us All

LAST OCTOBER, THE *LANCET* COMMISSION on Global Mental Health and Sustainable Development issued its promised ten-year reassessment. The recommendations are data-driven and ambitious. They need to be: The number of people across the globe affected by mental health disorders is staggering.

The World Health Organization estimates that 300 million people worldwide are affected by depression, 60 million with bipolar affective disorders, and 23 million by schizophrenia.

The Centers for Disease Control and Prevention report that in the United States, mental illness ranks third among causes of hospitalization for people between the ages of 18 and 44. Furthermore, 90 percent of those who die by suicide—the tenth leading cause of death in this country—have an underlying mental illness, according to the National Alliance on Mental Illness.

Our profession is not exempt. A 2016 *JAMA* meta-analysis of 167 studies of depression, depressive symptoms, and suicidal ideation in medical students, both preclinical and those in clinical rotations, reports that about 27 percent of those trainees screened positive for depression and 11 percent experienced suicidal ideation. Residents and practicing physicians are also at risk. Some estimates indicate double-digit rates of depression in these groups and suicide rates twice that of the general population.

Researchers are seeking to understand the molecular mechanisms of mental health disorders with the goal of developing therapeutics.

At HMS, efforts are underway to address mental illnesses directly. Researchers in Global Health and Social Medicine are actively engaged in developing and implementing training programs in mental health care and policy both in this country and internationally. Our Health Care Policy researchers are studying how health care systems and health care coverage serve people with mental illness while also weighing the quality of care they receive. Primary care investigators are piloting novel approaches that bring mental health assessment and care into everyday clinical practice.

In our laboratories, neurobiology and genetics researchers are seeking to understand the molecular mechanisms of mental health disorders with the goal of developing therapeutics. And among our affiliates, we have many world leaders in mental health research and care. Their innovative biological and clinical approaches to caring for those with mental health disorders change lives every day.

We seek to provide enhanced support for our students, too. Early in my tenure as dean, we established a task force charged with building and promoting programs that support mental health and wellness and provide access to advising, mentoring, and mental health resources.

Although the problem, as the *Lancet* Commission stated, is vast and complex, our community has the resilience, the scientific creativity, and the will to find solutions.

George Q. Daley
Dean of Harvard Medical School

HARVARD
medicine

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RANDY GLASS

"Aiken's perseverance and hard work now influence everyone on Earth."

Tape Recordings

IN THE WINTER ISSUE OF *HARVARD MEDICINE*, the terse caption on page two described an input tape for what was "dubbed the Harvard Mark I" electromechanical calculator, but did not say that the machine led to the "big data," described in other articles in the issue, that's now being harnessed by artificial intelligence in service to medicine. The caption continued a tradition of weak respect for the machine's inventor, Howard Aiken, a pioneer of digital electronic computers and, as such, one of Harvard University's great contributors to science and humanity.

The mention of the Harvard Mark I also refreshed a memory from my half-century career at Johns Hopkins Hospital when, in 1972, Aiken was a patient. The chief of private medicine asked me to show Aiken our new radiology computer reporting system; Aiken gave me lectures predicting the future of computers. Over the past thirty years, those lectures have proved to be amazingly accurate.

Aiken's brilliance was recognized in high school. An Indiana electric utility helped pay for his college and graduate education, where the long hours he spent on tedious calculations led him to the Babbage machine, a mechanical calculator designed in 1837.

Aiken thought that electronics could make the device work and floated the idea to two competitors: Monroe Calculator and IBM. Both turned him down, but Monroe's chief engineer advised him to stay close to IBM. He did.

In the 1930s, the U.S. Navy wanted a fast way to calculate the trajectory of ballistic missiles, and Aiken, then at the Harvard Computation Lab, got the grant. He collaborated with Grace Hopper and hired IBM engineers to make the Mark I, followed by the Mark II through V. The developments made IBM a computer giant.

Aiken was one of several Ivy League digital electronic computing pioneers. He is considered by many to be the dean of the field. His perseverance and hard work now influence everyone on Earth.

PAUL WHEELER, MD '61
STUART, FLORIDA

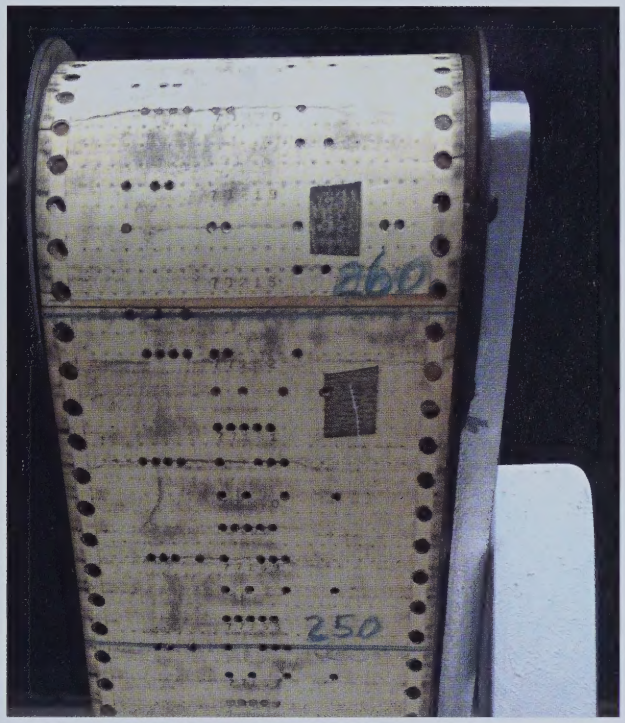
Ed: When preparing copy for the magazine, it's not uncommon for editors to feel they're trying to fit a world into a thimble. Fortunately, readers like Dr. Wheeler are out there, ready to help us tell the untold. We appreciate Dr. Wheeler's calling our attention to the contributions of Howard Aiken.

Encouraging Words

THANK YOU FOR THE *HARVARD MEDICINE* email in February in which you featured a response from an earlier issue to a "Rounds" question on mentors at HMS.

I would like to mention the name of Rudi Schmid, who played a fundamental and formative role in my career, beginning with an eight-week research experience in his laboratory when I was a third-year HMS student. Rudi, a recognized authority on porphyria, had been invited to investigate a new and unexplained epidemic of these disorders in Turkey. It seemed possible that they might be related to widespread exposure of the population to hexachlorobenzene, an agricultural fungicide, but such an etiology for this group of disorders had never been described. Rudi conducted some preliminary experiments that encouraged him to proceed in this direction.

It was my incredibly good fortune to have inquired about the availability of a summer research opening in his lab. Rudi's work during that period led to confirmation of his hexachlorobenzene hypothesis and publication in *Nature*. Rudi allowed me to be the first of two authors on that paper.



The program tape for the early electromechanical calculator known as the Harvard Mark I.

He also encouraged me to seek additional training in the laboratory of Kurt Isselbacher, MD '50, after completion of my residency in internal medicine. He then supported my application to Isselbacher's fellowship program. After I completed that fellowship, Rudi invited me to join his unit in the Department of Medicine at the University of California, San Francisco, where he eventually became director of the liver center, then dean of the UCSF School of Medicine.

My relationship with Rudi and his family was that of a friend and colleague. I am grateful for the profound influence he had on my career. In retrospect, I have been truly fortunate in my medical training and career.

ROBERT OCKNER, MD '61
ALISO VIEJO, CALIFORNIA

Ed: The "Rounds" section of Harvard Medicine *is a continual source of delight, for it allows us to present small stories from our alumni readers, stories that recount student life at HMS and, we hope, also rekindle memories among our alumni. Our thanks to Dr. Ockner for his remembrance of a mentor and friend.*

Alumni interested in responding to any of the questions posed in "Rounds" can do so at https://hms.harvard.edu/rounds.

Varied Effects

GENETIC VARIATION may influence the effects that various supplements have on individuals, say HMS scientists at Brigham and Women's Hospital. In a retrospective analysis of data from studies assessing vitamin E supplements and cancer risk, the researchers found that variations in the gene *COMT* influenced whether vitamin E decreased or increased risk of developing cancer during and after the study periods. *COMT* has three variants: met/met, val/met and val/val. The team found that met/met participants who took vitamin E had cancer rates 14 percent lower than similar participants taking a placebo. Among val/val participants who took vitamin E, cancer rates were 15 percent higher compared to rates in placebo-taking peers.

Hall KT, et al., *Journal of the National Cancer Institute*, January 2019

CANCER

Low-cost drug improves ovarian cancer outcomes

RESEARCH IN ANIMAL MODELS indicates that the hypertension drug losartan may improve the effectiveness of chemotherapy agents used to treat ovarian cancer. The work follows studies by the same team of HMS scientists at Massachusetts General Hospital that showed a similar effect for losartan in animal models of breast and pancreatic cancers. This earlier work led to a phase 2 clinical trial that had promising results against pancreatic cancer.

The new study could provide information and tools to explore a new therapeutic target for ovarian cancer, a disease that leads to the death of about 14,000 people in the United States annually.

Growing cancer cells produce extracellular matrix molecules that can compress blood vessels, diminishing the delivery of drugs to tumors. Losartan reduces such fibrous material, so the research team introduced it to the study animals to determine whether the drug affected blood supply and drug delivery to their ovarian tumors.

The team found that losartan treatment reduced extracellular matrix content associated with ovarian tumors and increased blood supply, oxygen levels, and drug delivery. In addition, the use of losartan in conjunction with the chemotherapy drug paclitaxel enhanced the antitumor effect of intraperitoneal paclitaxel and reduced the accumulation of fluid in the abdomen, a buildup that significantly reduces patients' quality of life.

A separate analysis of records of patients who received standard treatment for ovarian cancer at Mass General or Brigham and Women's Hospital while also being treated for hypertension found that patients taking losartan or other angiotensin-targeting drugs at the time of diagnosis lived an average of 30 months longer than those taking other hypertension drugs.

Diop-Frimpong B, et al., *PNAS*, January 2019

Immunology

Smoking cessation can delay, even prevent, severe form of rheumatoid arthritis

Analysis of data gathered over decades from two cohorts of the Nurses' Health Study has shown that a change in behavior, specifically stopping the smoking of cigarettes, reduces the risk of developing seropositive rheumatoid arthritis, the most common form of the disease. Women who had seropositive RA and permanently quit smoking showed the greatest drop in risk: 37 percent after 30 years.

Liu X, et al., *Arthritis Care & Research*, February 2019

CLINICAL MEDICINE

Heart disease risk linked to financial stress

CORONARY HEART DISEASE is the leading cause of death in the United States, and Blacks are disproportionately affected. Although researchers have investigated how financial hardship may influence health among Blacks, studies of associations between financial hardship and coronary heart disease in this population have been lacking.

Now, findings from a study by HMS researchers at Brigham and Women's Hospital have shed some light. In a study of cardiovascular disease risks among the Black population in the Jackson, Mississippi, area, researchers examined the association between the psychological stress of financial hardship and coronary heart disease and found that participants who experienced moderate to high financial stress had an increased risk of developing heart disease compared to those who did not report such stress. Data for this study were gathered from more than 2,000 participants in the Jackson Heart Study, a population-based longitudinal cohort.

Researchers analyzed data from 2000 to 2012 from participants who did not have evidence of heart disease at the beginning of the study. Participants were asked to rate their experience of stress in several areas. The severity of each finance-related stress was rated on a 7-point scale, which the researchers then used to categorize the total level of such stress participants reported at the onset of the study.

Researchers also assessed other participant characteristics and behaviors thought to lead to heart disease, whether participants had access to health care, and social issues such as participants' education and income. The mix of three key factors—depression, smoking, and diabetes—appeared to explain some of the connection between financial stress and heart disease risk.

Although the study showed an association, not a causal connection, between financial stress and heart disease risk, the researchers say the results should prompt deeper investigation into the role of economic stress on disease risk and encourage policies to reduce these stressors.

Clark CR, et al., *American Journal of Preventive Medicine*, January 2019

NEUROLOGY

Hearing loss may predict risk of cognitive decline

HEARING LOSS affects tens of millions of people in this country, and its global prevalence is expected to grow as the world's population ages. Increasingly, research indicates that such loss is associated with higher risk of cognitive decline. A recent study by HMS ››

›› investigators at Brigham and Women's Hospital adds to this body of evidence. Their findings also suggest that hearing loss may help identify individuals at greater risk of cognitive decline and provide insights for earlier intervention and prevention.

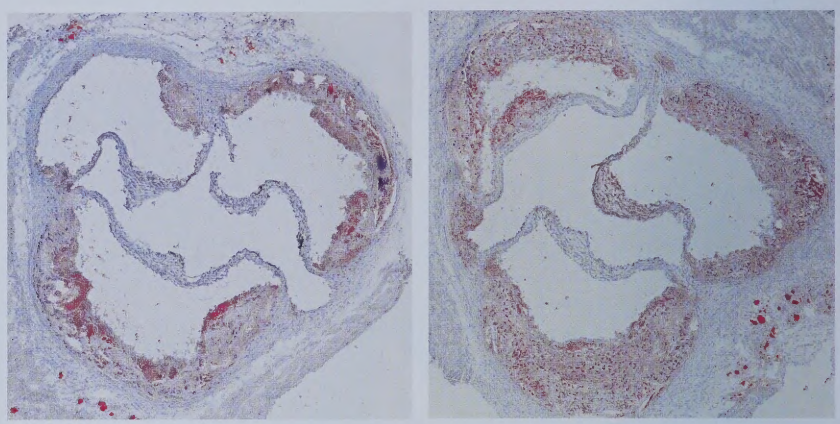
The researchers conducted an eight-year longitudinal study among more than ten thousand men aged 62 or older who were part of the Health Professionals Follow-up Study. The team assessed subjective cognitive function scores based on participants' responses to a six-item questionnaire administered in 2008, 2012, and 2016. Subjective cognitive function decline was defined as a new report of at least one such cognitive concern during follow-up.

The team found that hearing loss was associated with higher risk of subjective cognitive decline. Compared with men with no hearing loss, the relative risk of cognitive decline was 30 percent higher in men with mild hearing loss, 42 percent higher with moderate hearing loss, and 54 percent higher with severe hearing loss and no use of hearing aids.

When the researchers assessed whether the use of hearing aids might modify risk, they found some lessening of cognitive decline in men who used hearing aids, but their risk was not significantly different from that in those who did not use such aids.

The authors note that the study was limited to predominantly older white male health professionals and that further studies in other populations would be necessary. In addition, the study relied on self-reported hearing loss and subjective measures of cognitive function.

Curhan S, et al., *Alzheimer's & Dementia*, February 2019



Cross sections of aortas of mice that experienced normal sleep (left) and fragmented sleep show that disrupted sleep caused buildup of arterial plaques, which contribute to atherosclerosis.

MCALPINE ET AL. 2019/*NATURE*; PROF. P. MOTTA/DEPT. OF ANATOMY/UNIVERSITY "LA SAPIENZA," ROME/SCIENCE SOURCE (OPPOSITE)

CARDIOLOGY

Lack of sleep clogs arteries in mouse model

GETTING ENOUGH SLEEP IS KEY to good health, and studies have shown that insufficient sleep increases the risk of serious problems, including cardiovascular disease. Now, in research using a mouse model, HMS scientists at Massachusetts General Hospital have discovered a sleep-regulated mechanism that, when disrupted, can lead to an increase in the production of inflammatory white blood cells. These cells are known to be major contributors to atherosclerosis, the buildup of arterial plaques.

The scientists identified how hypocretin, a hormone in the brain known to control wakefulness, regulates both the production of inflammatory cells in bone marrow and the health of blood vessels. When sleep is insufficient or disrupted, levels of hypocretin decrease, resulting in a rise in inflammation and heart disease.

For its study, the research team repeatedly interrupted the sleep of mice genetically programmed to develop atherosclerosis. This was meant to simulate the experience of someone constantly waking up because of noise or discomfort.

Compared to animals from the same strain allowed to sleep normally, mice subjected to sleep fragmentation developed larger arterial plaques and had more monocytes and neutrophils—inflammatory cells that contribute to atherosclerosis—in their blood vessels. Further experiments revealed that the sleep-deprived mice had a nearly twofold increase in the production of certain stem cells in bone marrow that give rise to white blood cells.

The researchers found that hypocretin regulates production of white blood cells through interaction with neutrophil progenitors in the bone marrow. Neutrophils, in turn, induce monocyte production through release of a factor called CSF-1. Tests in mice lacking the hypocretin gene revealed that the hormone controls CSF-1 expression, monocyte production, and the development of arterial plaques. In sleep-deprived animals, the drop in hypocretin led to increased CSF-1 production by neutrophils, elevated monocyte production, and accelerated atherosclerosis.

McAlpine CS, et al., *Nature*, February 2019

HM INDEX: *AS PEOPLE AGE, THE RISK FOR ATHEROSCLEROSIS INCREASES, RISING IN MEN AFTER AGE **45** AND IN WOMEN AFTER AGE **55**.*

A Role for Fat

HMS RESEARCHERS at Joslin Diabetes Center have found that exercise dramatically changes fat, causing it to release an adipokine protein known as TGF-ß2 into the bloodstream. Although adipokines often are harmful to metabolism and health, the researchers found that, in mice, increased levels of TGF-ß2 in fat tissue and the bloodstream improved glucose tolerance and fatty acid uptake. The team also found that lactic acid, released from muscles during exercise, triggered the release of TGF-ß2 from fat. The findings suggest that TGF-ß2 may hold potential as a treatment for high blood sugar.

Takahashi H, et al., *Nature Metabolism*, February 2019

This colorized scanning electron micrograph shows adipocytes, the brown and yellow fat cells in the photo, amid adipose connective tissue fibers, which have a supportive function.

Shared Service

ALTHOUGH THE PRACTICE of overlapping surgeries, in which one surgeon, assisted by a surgical team, performs more than one procedure at a time by moving between operating rooms, has raised concerns, an analysis by researchers in the Department of Health Care Policy in the Blavatnik Institute at HMS has found that such surgeries create no greater risk for complications or in-hospital patient deaths than most single surgeries do. Exceptions are for high-risk patients and those undergoing coronary bypass surgery, where slight elevations in mortality and complications were found. Procedure duration, however, was notably longer for overlapping surgeries: 204 minutes, on average, compared with 173 minutes.

Sun E, et al., *JAMA*, February 2019

THE FUTURE OF MEDICINE

A letter from Len Blavatnik to the HMS community

I WAS HONORED to attend the dedication of the Blavatnik Institute at Harvard Medical School in February, and appreciate Dean Daley's remarks thanking the Blavatnik Family Foundation for its support of transformational research at HMS and of those who drive the School's scientific success.

I was raised in an environment in which science was respected and education was cherished. My father was a professor of chemistry, and my mother an electrical engineer who taught at a local university. Their interests inspired mine: in college, I focused on mathematics and physics and earned a degree in computer science. I've always been intrigued by science, and I enjoy speaking with scientists, discussing their work and ideas, and seeing their passion as they describe their research.

I've always sought to make an impact on the world in a large and meaningful way and to foster change that benefits society. My involvement with the community of HMS scientists is yet another opportunity to help accelerate innovation and discovery. In fact, this involvement may offer the greatest opportunity of all. The work done by HMS researchers has enormous potential to improve the lives of people throughout the world and to do so more quickly than thought possible.

Several years ago, I was given a poster that simply says: Think Big.

That poster remains in my office. Thinking big is how things get done and how we make positive change happen.

I look forward to visiting HMS often and to meeting many more of the dedicated HMS researchers and scientists making a difference in the world. Moreover, I look forward to learning about how you choose to think big in your work and to celebrating your many future discoveries.

Sincerely,
Len Blavatnik

SEE ALSO: LEN BLAVATNIK'S SIGNATURE (OPPOSITE)

noteworthy

Launch of medical school with singular focus is celebrated

The recent opening of the University of Global Health Equity in Rwanda marked the launch of the world's first medical school dedicated to global health equity. Attendees included Rwanda's President Paul Kagame; Vice Chancellor Agnes Binagwaho, the school's leader and a senior lecturer on global health and social medicine in the Blavatnik Institute at HMS; Abebe Bekele, the school's dean; and HMS representatives Dean George Q. Daley, MD '91; Paul Farmer, MD '90, PhD '90; and environmental medicine leader Philip Landrigan, MD '67.

The university was spurred by Partners In Health, which Farmer (*fig. 1*), the Kolokotrones University Professor and chair of the Department of Global Health and Social Medicine in the Blavatnik Institute at HMS, co-founded and is chief strategist for.

The new medical school is located in Butaro, which in 2008 was one of the poorest regions in Rwanda and, until 2011 when Butaro Hospital opened, was the only district in the east African nation without a hospital. Both the hospital and its Cancer Center of Excellence were integrated into a health system that partnered with community health workers and village clinics, helping Butaro register the fastest decline in premature mortality from infectious disease ever recorded, with under-five mortality dropping by 60 percent over five years.

Under the leadership of Binagwaho and Bekele, the school's educational efforts will work to relieve shortages of health care providers and researchers in low-resource settings. The first class of medical students is scheduled to enter in 2019 and graduate as medical doctors in 2025. All of the university's graduates will earn joint degrees in global health delivery, toward the goal of developing a corps of clinician-researchers who can implement new programs, examine the results, and use research-driven evidence to improve global health delivery, school leaders said.

In his remarks, Daley noted that the recently updated HMS mission statement emphasizes that the School's community is "dedicated to alleviating suffering and improving health and well-being for all." It is an aspiration, he said, that HMS shares with Rwanda's new university.

Alumni leaders in industry gather to connect and learn

In early February, the HMS Office for External Education's Executive Education program hosted the first Harvard Medical School Alumni in Industry Summit. The gathering drew more than sixty alumni, representing a span of roughly forty-five graduation years, to campus. According to Associate Dean for Executive Education Stanley Shaw, MD '95, PhD '95, the event recognized an often-overlooked HMS alumni cohort.

"Many felt that the time for recognizing alumni who are contributing to innovation in health care through an industry role—ultimately trying to improve the care of our patients—was long overdue," says Shaw (*fig. 2*). "We thought that convening this meeting could help alumni make new connections and learn from one another. The alumni were thrilled to come back to the School. There was a wonderful spirit of camaraderie and fellowship."

The summit's keynote was delivered by George Q. Daley, MD '91, who outlined the School's therapeutics initiative and described its general efforts to foster more collaboration between HMS faculty and industry. Panel discussions delved further into academia-industry collaboration, with panelists analyzing the various paths physicians can take when moving from the halls of the academy to those of industry, translating the values learned at HMS into corporate life, and exploring the future of health care through the lens of industry.

Some current HMS students attended, many hoping for advice on pursuing a nontraditional career path. From these interactions, says Shaw, there developed a "great interest among the alumni for nucleating a more formal mentoring network for students." Details for such a network, as well as for the next summit, are now being discussed.

fig. 1

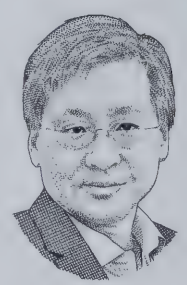


fig. 2

fig. 3

"I think from this event will grow a better understanding of the community of HMS alumni working in industry," says Shaw. "We know we're not yet reaching everybody who's out there, but we know our alumni are shaping the future of health care through their leadership."

Student-built mentoring tool aids in navigating career choices

A pair of first-year students were feeling a sense of pressure over decisions concerning their medical career. They knew the choices were out there but were overwhelmed by the number of them. Guidance was needed (*fig. 3*), especially guidance that would offer a personal connection with someone of common interests.

That's when the idea for Weave, a digital mentorship platform to connect HMS students with faculty members who have similar interests or identities, took root.

Development work on the platform started in early 2017, first by researching the idea, then with surveys to students and faculty. Various faculty were interviewed to more fully understand their interests and perspectives on mentorship and its intersection with faculty development. The building of the Weave website began early in 2018.

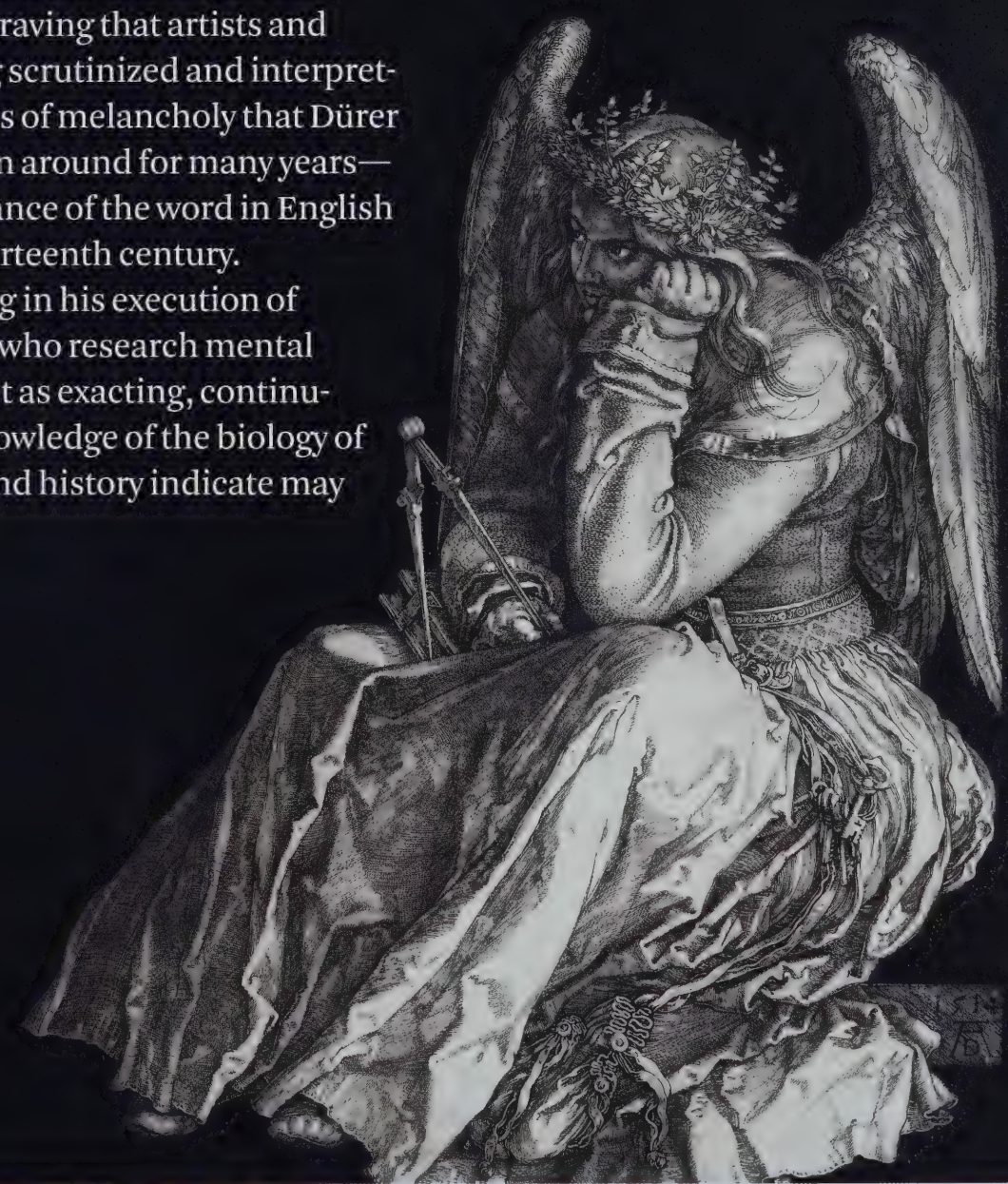
Weave can be found at **weave.hms.harvard.edu**. It opened to faculty registration in December 2018 and already has nearly one hundred faculty profiles. It opened to student registration in January.

Although all Weave-mediated collaborations begin with a shared interest, they can broaden to become academic- or career-oriented. Plans for the future of the platform include peer-to-peer mentoring options as well as expansion to include residents, staff, and alumni as mentors.

The Roots of Mental Illness

In the early 1500s, the German artist Albrecht Dürer incised dejection and darkness, symbol and metaphor into metal. The result was *Melencolia I*, an engraving that artists and scientists have long scrutinized and interpreted. The descriptions of melancholy that Dürer drew upon had been around for many years—the earliest appearance of the word in English dates to the late fourteenth century.

Dürer was exacting in his execution of *Melencolia I*. Those who research mental illness today are just as exacting, continually refining our knowledge of the biology of disorders that art and history indicate may be deeply etched.



Albrecht Dürer
Melencolia I, detail
1514
Engraving
Collection of the National Gallery of Art


STRUCTURE OF A NEURON
Dendrites
Synaptic Cleft
Dendrite
Axon Terminal
Cell Nucleus
Axon
Myelin Sheath
HEAD
COLLAR
TAIL
END PLATE
TAIL FIBER
Memory.

DUNG HOANG

Bring to Light

Researchers are unearthing the biological roots of psychiatric disorders

BY STEPHANIE DUTCHEN

A CENTURY OR TWO AGO, IF A patient developed a persistent cough, physicians could only approximate the cause and offer a suppressant. Today, a deeper understanding of the many distinct biological origins of cough, combined with better diagnostic and treatment tools, allow doctors to zero in on a patient's specific problem—be it asthma, an infection, or lung cancer—and prescribe the remedy that targets the underlying pathology.

While fields such as cardiology and oncology have made similar strides, psychiatry has lagged behind. Researchers haven't yet pinpointed the biological causes of major psychiatric and neurodevelopmental disorders, including schizophrenia, bipolar disorder, and autism spectrum disorders. There are no physical tests to diagnose or chart the course of these conditions. With the roots unknown, treatments can address only symptoms.

Change now brightens the horizon. Equipped with sophisticated tools and an ever-greater understanding of the human brain, researchers are at long last identifying biological phenomena—including gene variants, molecules, cell types, neural circuits, and inflammatory and metabolic processes—that may underlie some of the more vexing maladies of the mind.

"Psychiatry still has a reputation as being fuzzy and only Freudian," says Kerry Ressler, MD '97, PhD '97, an HMS professor of psychiatry, chief scientific officer at McLean Hospital, and former president of the Society of Biological Psychiatry. "Many people don't appreciate how much progress we've made even in the past few years in understanding the biological basis of behavior and how that goes awry in what we call mental illness. We're in a transformative period in neuropsychiatry, and we now believe that these problems, though enormously complex, are finite and solvable."

Unmasking biological contributors promises to improve the classification, diagnosis, prognosis, screening, and treatment of psychiatric disorders and open the door to prevention and treatment. It could also reduce the stigma that has beleaguered people with mental illness and neurodevelopmental disorders for centuries.

If researchers are able to provide physiological explanations and, crucially, translate them into more effective care, hundreds of millions of people worldwide could benefit. Nearly 20 percent of adults, roughly 65 million people, in the United States live with a mental illness, according to the National Institute of Mental Health. About one-quarter of those cases constitute serious psychiatric illnesses: disorders of thinking, behavior, or feelings that significantly impair function. Mental illnesses cause more disability and death in people under age 50 than any other group of disorders, reported Thomas Insel, former director of NIMH, in *New Scientist* in 2015.

Biological insights won't tell the complete origin stories of psychiatric and neurodevelopmental disorders. Traumatic experiences, grief, stress, substance use, and an array of other environmental and cultural factors play important roles as well. The onset of post-traumatic stress disorder requires an external trigger, but differences in genetics, biochemistry, or neural circuitry may explain why some people develop debilitating fear after a traumatic event while others do not.

Similarly, treatments that follow from biological discoveries are expected to complement rather than replace other effective strategies. Studies might indicate which patients would benefit most from combining talk therapy with medications, ideally those developed from newly identified molecular targets.

"We haven't developed any drugs for schizophrenia that represent a different molecular target or pathway than the drugs that were discovered in the fifties and sixties," says Aswin Sekar, PhD '14, MD '16, a former HMS genetics graduate student who will rejoin the community in July as a hematology-oncology fellow. "It's hard to change that situation without understanding the biological mechanisms underlying the disease."

A million tiny pieces

Studies in twins have led researchers to estimate that schizophrenia, bipolar disorder, and autism spectrum disorder are 60 to 80 percent heritable, meaning that across a population, the majority contribution to these conditions comes from parental DNA sequences or expression patterns. PTSD is thought to be 30 to 50 percent heritable in those who have experienced trauma. For all these conditions, the remaining percentage encompasses everything else, from spontaneous gene mutations to differences in brain anatomy to individual traumatic experiences.

Although genetics can contribute substantially to psychiatric disorders, finding and acting on the culpable variants or mutations has been difficult. That's in part because there is no single driver like the *HTT* gene mutation known to cause Huntington's disease. Instead, there are a variety of genes that each raise risk a small amount. Several hundred gene locations have been implicated in schizophrenia so far.

In 2016, Sekar, then a member of the lab of Steven McCarroll, the Dorothy and Milton Flier Professor of Biomedical Science and Genetics in the Blavatnik Institute at HMS, found a gene variant that raises a person's risk for schizophrenia from about 1 percent to 1.25 percent.

Researchers also want to know how such genes influence disease. McCarroll's team determined in postmortem human brain tissue that different common variants (alleles) of the gene *C4* make different amounts of a protein called C4A and that the variants that make C4A were all more common among people with schizophrenia. Then, in work in mice, McCarroll's colleagues Beth Stevens, an HMS associate professor of neurology at Boston Children's Hospital, and Michael Carroll, an HMS professor of pediatrics at Boston Children's, showed that *C4* tags synapses for pruning during brain development. Taken together, the findings suggest that schizophrenia involves excessive synaptic pruning via C4A and perhaps other such proteins.

The study was hailed worldwide, with some scientists saying it offered an explanation for why people with schizophrenia have thinner tissue in the prefrontal cortex and thus difficulties with behaviors governed by this region, such as executive function, social behavior, emotional response, and personality expression. Furthermore, because synaptic pruning occurs as people mature from adolescence into adulthood, the findings could illuminate why schizophrenia typically manifests in the teens or early twenties.

Building on such findings will be no easy task, considering that many diseases with much simpler genetics still lack treatments. Still, McCarroll, who is also the director of genomic neurobiology in the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, says having many small risk factors offers an opportunity.

"What excites me isn't 'small,' it's 'many,'" he says. "You may not have one big genetic shove, but you can investigate whether multiple nudges act on the same cell populations or cellular processes. I think that's what will teach us how these illnesses work and how to treat them."

"We haven't developed any drugs for schizophrenia that represent a different molecular target or pathway than the drugs that were discovered in the fifties and sixties."

Scent trail

Gene variants aren't all that can be inherited when it comes to psychiatric disorders.

As part of his research into normal and disordered fear learning, Ressler has found that not only do mice that repeatedly experience a mild shock combined with a scent react with fear when later exposed to the scent alone but so do their offspring and their offspring's offspring. He discovered that areas of the mice's brains involved in olfaction undergo structural and functional changes that get passed down as well.

Further experiments indicated that the mouse version of exposure therapy—smelling the scent ninety times over three days without any shocks—reduces the fear response and reverses the neural changes in their brains as well as potentially in their offspring.

Ressler and colleagues hope this line of inquiry will ultimately inform treatment for patients with PTSD who suffer extreme reactions to scents associated with traumatic memories, such as the cologne worn by someone who once abused them.

Parallel efforts are uncovering molecules, signaling pathways, cell types, and neural circuits involved in the creation, suppression, and overall plasticity of fearful memories. Researchers, including Ressler, are exploring ways to prevent new memories from being encoded with excess fear after a traumatic event by taking advantage of a brief window of malleability before the memory consolidates. For established memories, the researchers are testing drugs that enhance neuroplasticity so clinicians can better help patients with PTSD gradually disentangle excess fear from traumatic recollections.

Outside influence

Of increasing interest in many disorders is the potential role of inflammation, the body's immune response to perceived threats.

Epidemiological studies suggest that pregnant women hospitalized for infections are more likely to give birth to children with certain psychiatric disorders, such as schizophrenia and major affective disorder, as well as with neurodevelopmental abnormalities, including autism spectrum disorder. The type of infection—influenza,

rubella, bacterial pneumonia, toxoplasmosis—doesn't seem to matter.

How maternal inflammation might lead to such issues in children, or whether the occurrences are coincidental, remains unclear.

Among those trying to connect the dots is Jun Huh, an assistant professor of immunology in the Blavatnik Institute at HMS. Using a mouse model of autism, Huh has implicated a particular type of immune cell and found a missing link in an unexpected place: the gut microbiome.

Huh discovered that provoking immune responses in pregnant mice can alter brain structure and neuronal activity in offspring. The changes resemble lesions seen in the prefrontal and temporal cortices of autistic children, although in the mice the changes occur in the primary somatosensory cortex. Many of the offspring also behave in ways analogous to autism, Huh found, such as spending less time socializing with other mice and more time engaging in repetitive acts such as burying marbles. The problems manifest in offspring only if infection occurs during a narrow window late in the first or second trimester.

Huh's research further revealed that if certain gut bacteria known to promote the biogenesis of T helper 17 immune cells are present in pregnant mice, infection can cause these immune cells to become overstimulated and produce an excess of cytokine IL-17a. Noting that fetal mouse brains have receptors for IL-17a, Huh postulates that activation of these cells starts the observed structural and behavioral changes. Blocking Th17 cells, or IL-17a or its receptor, reversed those changes.

Provoking immune responses in pregnant mice can alter brain structure and neuronal activity in offspring.

To find out whether similar variations in the human microbiome drive at least some cases of autism, Huh is setting up collaborations with clinicians worldwide to analyze stool samples from women who were or were not sick during pregnancy and who have children with autism. He envisions a day when individuals hoping to become pregnant can be screened for risk of adverse immune reactions and, if found at risk, provided either a currently available Th17 cell blocker or a new immunotherapy to prevent any reactions.

"I think inflammation plays a larger role than people have appreciated," says Huh. "I hope our studies get people excited to focus on the maternal side as well as on children."

High on the list of caveats for studies like these is the question of how well mouse or other animal behaviors reflect the actions and experiences of people with neurodevelopmental and psychiatric disorders. "Is what we're seeing in our model comparable to autism?" asks Huh. "Probably, but only time and further research will tell."

Limitations in animal models have hampered research into psychiatric disorders that involve issues of interiority or occur in evolutionarily advanced parts of the brain. As Sekar points out, some experiences may be uniquely human.

Collected wisdom

Although many findings in biological psychiatry still lie within the realm of correlation, that might be enough to move ahead.

"We don't have to know the whole sequence of events in order to intervene," says Dost Öngür, MMSc '07, the HMS William P. and Henry B. Test Professor of Psychiatry and chief of the Psychotic Disorders Division at McLean Hospital.

"Psychiatry is full of successes like that. We don't actually have the explanation for why people with depression have a serotonin deficiency, but SSRIs still work for many people."

Before Ressler came to McLean, he helped build a cohort of more than 12,000 residents of inner-city Atlanta to study civilian trauma and PTSD. In one study that followed a subset of this cohort, Ressler's

Dost Öngür is designing a clinical trial to help determine whether the buildup of oxidative stress molecules found in the brains of patients with schizophrenia and bipolar disorder is a by-product of the illnesses or contributes to their cause.

team found that people with chronic PTSD who take blood pressure medications that act on the hormone angiotensin have less intense psychiatric symptoms. Curious, Ressler and colleagues went on to uncover angiotensin receptors in the amygdala, the brain's fear center, leading them to propose that angiotensin joins adrenaline and cortisol in managing the body's stress response. Bolstered by mouse studies and genetic analyses, he's now testing losartan, a common angiotensin-receptor blocker, as a PTSD treatment in a multisite randomized controlled clinical trial funded by the U.S. Department of Defense.

Using magnetic resonance spectroscopy, Öngür has documented significant metabolic problems in the brains of people with schizophrenia and bipolar disorder: the synthesis of the energy storage molecule ATP is slower by 22 percent than in healthy brains and generates excess "exhaust fumes" in the form of oxidative stress molecules. Although it isn't clear if the problems, which have been spotted in other diseases such as Alzheimer's and epilepsy, are effects of or contributors to psychotic disorders, Öngür thinks addressing them could improve patients' cognitive load. Now he's translating those findings into a clinical trial.

The imaging work represents one way that researchers are trying to transform traditional, arguably subjective, gauges of psychiatric illness into more quantitative measures. "We currently have no way to measure the neural basis of psychopathology," says Ressler.

Another strategy involves seeking biomarkers that can help distinguish different stages and courses of illness. Solid results could allow psychiatrists to offer prognoses, whereas now it's impossible to predict how a patient will progress. For instance, no one knows why some people diagnosed with schizophrenia do well while others follow a "relentless downhill course," says Öngür. Both at McLean and as part of the Massachusetts Psychosis Network for Early Treatment, he is helping to tackle the problem by collecting, standardizing, and analyzing data from patients with psychosis starting from their first episode.

Taxonomy

By illuminating differences within and among psychiatric and neurodevelopmental disorders, biological insights could also inform the way these illnesses are classified, a perennial thorn in psychiatry's side.

Much as cancers were once defined by the organs where they first appeared but are now more accurately diagnosed and treated based on molecular characteristics, what clinicians currently call schizophrenia or autism may prove to be collections of disorders distinct enough to require different approaches. Conversely, there may be unforeseen connections between disorders assumed to be unrelated.

"Do we even know what these disorders are?" asks Öngür. "Nobody thinks schizophrenia is one thing. Nobody thinks our diagnostic categories are great, but nobody has anything better."

Large-scale efforts such as NIMH's Research Domain Criteria project are gathering genomic, cellular, imaging, and behavioral information from people with mental illnesses and running analyses in an attempt to let categories arise from the data. Such projects remain in the early stages.

Genomic analyses, meanwhile, are turning up overlaps and divergences that alternately support and challenge standard classifications as researchers seek the disorders' underpinnings. A 2013 study led by Jordan Smoller, MD '92, an HMS professor of psychiatry at Massachusetts General Hospital, found that autism, schizophrenia, bipolar disorder, depression, and attention-deficit hyperactivity disorder share gene variants, while a 2018 analysis by UCLA researchers found that although bipolar disorder is characterized as swings between mania and depression, its gene-activity patterns in the cortex resemble schizophrenia more than depression.

Studies of brain circuitry offer refinements as well. Researchers comparing the neural patterns of people with and without schizophrenia have seen abnormalities in the circuit connecting the auditory cortex to other parts of the brain, suggesting why people with the disorder are more likely to have trouble distinguishing which voices come from their own thoughts versus the outside world. By studying the same circuits within schizophrenia, comparing patients who experience auditory hallucinations to those who don't, Öngür and colleague Ann Shinn, MMSc '11, an HMS assistant professor of psychiatry at McLean, tied those abnormalities to the group with hallucinations. They replicated their findings in bipolar disorder.

When it comes to causes, mechanisms, and treatments, the field is firmly rooted in the body.

"This is something that travels with hallucinations, not with a diagnosis," says Öngür.

Arc of discovery

Researchers like Öngür and McCarroll see themselves in the nascent stages of understanding the roots of psychosis, while scientists like Ressler who work on more primitive and well-studied phenomena believe they're near the middle of an arc that ends in effective, biologically informed treatments.

Scientists are both optimistic and braced for a hard road ahead, given the complexity and mystery of behavior and cognition. How does a malfunctioning circuit contribute to the ineffable phenomenon of delusion? As Siddhartha Mukherjee, MD '00, when writing about the *C4* gene discovery in *The New Yorker*, asked: How does synaptic overpruning beget emotional emptiness?

Will we ever know? Do researchers first need to crack the age-old question of how the body gives rise to consciousness, to self?

Of course, when it comes to causes, mechanisms, and treatments, the field is firmly rooted in the body. Because postmortem brain samples from people with bipolar disorder or autism don't present the same striking anatomical abnormalities as the plaques in Alzheimer's disease or the loss of medium spiny neurons in Huntington's, says Sekar, uncovering the biological mechanisms of psychiatric and neurodevelopmental disorders may require a deeper look.

"We believe as biologists that if it's an illness with an organic, molecular cause, then the information must be in the tissue somewhere," says McCarroll. "The molecular secrets are probably still hidden."

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.

Line of Sight

BY ANN MARIE MENTING

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Borderline Personality Disorder
2018
Korean ink on Korean paper
48 x 72 cm

Confusion and frustration prompted a physician to study a mental illness that many considered impossibly enigmatic

During his residency at Massachusetts Mental Health Center in the late 1960s, John Gunderson, MD '67, was troubled by a type of patient that he and his colleagues would see regularly. Nearly all of these patients came in following a suicide attempt. All were angry, very angry, and all would complain about being mistreated by or alienated from members of their family or their romantic partner. They created, he said, significant problems for the staff.

"We didn't have a diagnosis for them," said Gunderson, during an interview shortly before his death in January. "The half of us who felt these people needed our sympathy would diagnose them with depression. Those of us who disliked them classified them as atypical schizophrenics, seeing them as manipulative. We'd try to get them out of the hospital quickly. To the patients, this only confirmed their sense of being mistreated and rejected, further worsening their condition."

"We misdiagnosed them, misunderstood them, and mistreated them," he added. "I felt frustrated because I was one of those people who vacillated."

Gunderson, who retired in 2018 from his role as director of the McLean Borderline Center, entered psychiatry at a time when evidence-based research in the field was on the ascent. Early in his residency he began a major research project to determine the effectiveness of psychoanalysis for schizophrenia. At the time, he thought it might validate the psychoanalytic approach used by his mentors to treat patients with schizophrenia. It proved the opposite.

"I showed it wasn't particularly effective for those with schizophrenia," said Gunderson. "My findings were disillusioning but informative. They allowed me to step back from psychoanalysis and realize the need to empirically prove the efficacy of treatments, to not stand on the merits of tradition and endowed wisdom."

It is estimated that borderline personality disorder is found in 1.7 percent of the general population.

With eyes newly opened, Gunderson conducted a small study at Mass Mental Health designed to characterize what some described as "wastebasket" patients. His drive to understand these patients grew and by the early 1970s, as a research fellow at the National Institute of Mental Health, he was collaborating on research to create diagnostic criteria that distinguished them from patients with schizophrenia. That work was followed by a literature review, "Defining Borderline Patients: An Overview," coauthored with clinical psychologist Margaret Singer and published in 1975 in the *American Journal of Psychiatry*. He then embarked on a collaborative effort to develop a structured interview that would ensure reliable diagnoses of the disorder and also provide a set of discriminating characteristics. By 1980, borderline personality disorder was included in the *DSM III* as a distinct personality disorder.

The field began to recognize Gunderson's pivotal work. He went, he said, from being "a failure as a treater to an expert on a group of patients that really confused and disturbed me." For nearly five decades, he continued to study this disorder, leading many to consider him its "father."

Throughout the decades, Gunderson innovated, developing a supportive intervention that involved families; describing children with the disorder as exhibiting interpersonal hypersensitivity, a characterization that incorporated genetics into the psychological theory of the disorder; and developing a new therapeutic approach called general psychiatric management. Many consider this generalist model especially notable because of its potential to serve the public health needs of patients with the disorder.

Among the psychotherapies considered effective for borderline personality disorder, dialectical behavior therapy has been the leading, and best-studied, one. It has been shown to significantly reduce patients' need for additional treatments such as hospitalization or medication and to decrease episodes of self-harm or suicide by half. Furthermore, research has shown patients who underwent this therapy maintained their improved status for between two and five years. The approach, however, calls for the patient to commit weekly to more than five hours of individual and group therapy and requires therapists to participate in two five-hour trainings.

General psychiatric management, by contrast, requires a single hour of individual consultation each week; caregivers need only participate in a one-day workshop to gain or hone the skills needed to supervise therapy. Although general psychiatric management has not been studied as much as its dialectical cousin, a major randomized controlled trial has shown it to be as effective as high-quality dialectical behavior therapy. In 2016, the *American Journal of Psychiatry* published a paper by Gunderson in which he "served notice of the emergence" of this model. Notice was taken: A few years ago, Gunderson said, a sixty-page clinical guide for this therapeutic approach began to be distributed to U.S. medical residents.

Broadening the understanding of borderline personality disorder and arming physicians with a therapeutic intervention is necessary given the prevalence of this illness. It is estimated that the disorder is found in 1.7 percent of the general population, 6 percent of primary care patients, and between 15 and 28 percent of patients in psychiatric clinics or hospitals. Recent heritability studies, which Gunderson drew upon when constructing his interpersonal hypersensitivity theory, indicate the variance associated with genetic factors is between 42 and 68 percent, a range similar to that for hypertension.

Reflecting on a career spent researching this disorder, Gunderson considered his to have been a most rewarding one. "I've been a part of a small army of people who intently engaged in this work. I have loved it." HM

Ann Marie Menting is the editor of Harvard Medicine *magazine.*

The healing profession is taking a clear-eyed look at depression within its ranks

DANIEL BEJAR

Safety Net

BY SUSAN KARCZ

THE REACTIONS OF FAMILY and friends to the news that he was going into psychiatry left Nathaniel Morris, MD '16, with the impression that he was somehow wasting his education. But the real surprise, he wrote in the *Wall Street Journal* in 2016, came as he was interviewing for residency programs and was assured that psychiatry was respected, just like any other department in their hospitals. The need to even mention this gave Morris pause.

Stigma still swirls around mental illness, even within the medical profession. Research has shown that medical professionals do not differ significantly from the general public in their views of patients with mental illness. In fact, some evidence shows that their beliefs and attitudes can be even more negative than those outside of medicine.

Morris, now a resident physician in psychiatry at Stanford University School of Medicine, has more than a professional interest in physician depression. While still in medical school, he started writing essays and blog posts for various publications on topics in medicine. Writing in the *Washington Post* one week before his graduation, Morris wrote of taking a quiz that would tell him if he met the criteria for depression.

He did.

He sought and received help, with good results, but only after he tearfully admitted to his advisor that he was not okay.

Leonard Su, a former vascular surgeon in Seattle, probably would not have considered taking such a quiz; he was convinced that despite the unrelenting abusive voices in his psyche, he couldn't be depressed.

"My inner voice was incredibly hateful and kind of spiteful so that no matter what I did, it was always negative," says Su. "I had this idea that depressed people didn't do anything, that they sat in a dark room or didn't get out of bed, so because I was doing

so many things, I couldn't be depressed." Su ended up leaving medicine after ten years as a surgeon and now speaks publicly about his own mental illness and the importance of destigmatizing such disorders.

Efforts are underway to break through many of the obstacles that impede our understanding of how physicians and physicians in training are affected by mental illness. Increasingly, the profession is looking inward, charting better ways to define and measure such illnesses, evaluating the effect of physicians leaving medicine because of depression and burnout, determining what kinds of supports medical schools and training programs should offer students and trainees, and addressing the persistent stigma of mental illness within the profession and outside of it.

Who, me?

Negative attitudes toward mental illness are particularly concerning to those in a caregiving profession. It has long been almost taboo among physicians to admit to having a problem, and even today, having depression or another form of mental illness can be talked about in hushed tones.

Many medical professionals fear having a record that shows they sought help—a fear that may be well-founded. The medical licensing applications for thirty-two states still contain questions about a history of mental health problems. Such questions may violate the Americans with Disabilities Act. An example from New Hampshire's application, which, according to a *Journal of the American Academy of Psychiatry and the Law* article in 2018, is not consistent with ADA regulations, asks, "Have you ever had any physical, emotional, or mental illness which has impaired or would be likely to impair your ability to practice medicine?"

The medical licensing applications for thirty-two states still contain questions about a history of mental health problems.

In physicians, the presence of depression is at least as common as it is among the general population, that is, 7 percent of U.S. adults; and, like anyone else, physicians are not good at recognizing the problem in themselves.

On top of that, physicians are notably reluctant to seek help for any illness, never mind depression. Physicians aren't trained to be "physician's physicians," and getting help from colleagues can be a difficult ask.

All this can lead to untreated depression, which raises the short-term risk for suicide and the long-term risk for repeated depressive episodes. Because physicians have access to and knowledge of the means to end their life, they have a suicide completion rate estimated at twice that of the general population, according to a 2018 report published in *Medscape*.

Students and physicians in training, new to their careers and in a highly competitive environment, are even less likely to admit that they have a problem.

Deep dive

The scope of depression can be difficult to pin down. Definitions are sliced differently and, probably even more relevant, there is a lack of standardized measurement tools.

Douglas Mata, an HMS clinical fellow in pathology at Brigham and Women's Hospital, became interested in depression and suicide in interns and residents after two of his former classmates died by suicide. Preparing to write a paper with researchers on the Intern Health Study out of the University of Michigan, a longitudinal cohort study looking at stress and mood in medical interns, he found that there was no published review summarizing the knowledge about depression in residents. He determined he would write his own.

"I'm going to find every single study that's ever been published that measured depression in resident physicians, and I'm going to combine all the data from those studies and create an overall answer," he recalls thinking.

And he and colleagues did, reporting in *JAMA* in 2015 that across the fifty-four studies they analyzed, the prevalence of depression or depressive symptoms ranged from 20.9 percent to 43.2 percent, depending on the measurement tool used. In addition, between 1963 through 2015, the years of the studies that were reviewed, prevalence grew modestly. Overall, the researchers reported a summary estimate of 28.8 percent prevalence among residents for screening positive for depression.

In a study published in 2016 in *JAMA* on depression and suicidal ideation in medical students, Mata and Lisa Rotenstein, MD '17, a clinical fellow in medicine at Brigham and Women's, found an overall prevalence of 27

"It's constructive to think about the systemic issues that contribute to burnout and depression."

JOHN SOARES

Lisa Rotenstein

percent for screening positive for depression and of 11 percent for suicidal ideation. Of those who screened positive for depression, the authors note, only 15.7 percent had sought treatment.

Internal combustion

A familiar, and related, phenomenon, burnout, also figures into the depression and suicide equation. Burnout, first noted in the scientific literature in the 1970s, is defined as having three components: emotional exhaustion, depersonalization or detachment, and a sense of personal ineffectiveness. Unlike mental illness, which is often considered a personal failing, burnout is thought of as a work-related syndrome and is thus less stigmatized and pathologized than depression, not only in medicine, but across professions.

Research published in *Mayo Clinic Proceedings* in February compared the prevalence of burnout and work-life satisfaction in physicians with that in a probability-based sample of the U.S. working population and found that, while physicians' risk of burnout is higher than in other professions, their prevalence of burnout decreased during the years studied, 2011 to 2017. In contrast, symptoms of depression in physicians increased during the same period.

Another study, published in *PLOS One* in 2016, showed that the more affected a physician was by symptoms of burnout, the greater their chance of also having depression, a finding that led the researchers to postulate that burnout may be a form of depression.

Rotenstein started studying burnout because of her interest in the business side of medicine and in exploring what she calls the workforce implications of depression and burnout in medicine. "People are more likely to cut back on hours worked. Burnout is associated with worse clinical care. I wanted to be able to understand the phenomenon from a care-delivery perspective as well," she says.

Another question she is looking at is whether burnout is an individual problem or a systemic one.

"It's constructive to think about the systemic issues that contribute to burnout and depression," says Rotenstein. "It gives us a completely different set of levers by which to solve the problem. It also helps us avoid a culture of blame, of individual blame."

Should we worry if some physicians leave the profession because of its challenges? Consider what is lost when a physician leaves medicine: the experience and skills of a talented health professional, the investment in training and the financial burden of replacing that individual, and the sundering of physician-patient bonds followed by the need to redistribute the patients left adrift. This loss is compounded when physicians of color leave the profession, as research has shown that these physicians are more likely to practice in underserved communities.

Getting picked for the team

Medical education and training programs, especially the most competitive, are objectively stressful and demanding. And, as in any challenging environment, some people thrive while others struggle. There are individual traits that can contribute to risk for depression, such as anxiety, perfectionism, impostor syndrome, cynicism, and being a "high control" person, as well as environmental factors such as long hours, loss of autonomy, less time with patients, ethical issues, and economic worries.

One study found that 39 percent of the participants scored on a validated depression scale as having symptoms of moderate to severe depression.

Environmental factors affect everyone in medical training, but how do you know which students will need help?

In a letter published in *Medical Education* in 2015, Mata suggested one way to remove some of that guesswork. Before the start of clinical training, he wrote, students could be assessed for their risk of depression using the thirteen-question sense of coherence scale, which assesses how people manage stress.

While they may have some unique stressors, physicians are not the only ones in medically related fields who face occupational stress. Veterinarians and dentists share similar risks of depression and suicide as physicians. And studies of students in graduate programs in several disciplines show a similar prevalence of depression.

One study of 2,279 graduate students from 26 countries and 234 institutions of higher education, published in *Nature Biotechnology* in 2018, found that 39 percent of the participants scored on a validated depression scale as having symptoms of moderate to severe depression. The authors add that transgender and gender nonconforming students face increased risk for depression over their gender-conforming counterparts, 57 percent, compared with 41 percent (females) and 35 percent (males).

A study in 2015 in the *Journal of Racial and Ethnic Health Disparities* compared risk for depressive and anxiety symptoms by race and gender in first-year medical students in the United States. Among factors that added

Nathaniel Morris, a frequent columnist for publications such as the *Wall Street Journal* and the *Washington Post*, has written about depression within the medical profession.

ELISABETH FALL

to the risk of depression and anxiety in the students was "stereotype threat," defined as a "disruptive psychological state" in which individuals bear the stress of being seen as confirming negative group stereotypes.

An unexpected finding of this study was that Black women did not end up with a double dose of risk; rather, the researchers found an interaction effect suggesting that Black women were at "slightly less risk for depressive symptomology and anxiety than would be expected given the main effect of race and gender."

While women and Black students in this study were at higher risk for depression and anxiety than their male and white counterparts, women generally had more social supports and coping skills than men, say the researchers, leading them to note that the "effect of race on social support changes depending on the gender of the medical student."

Light source

There are reasons to be optimistic about early interventions and prevention. Mental health is beginning to be more openly discussed and taken seriously as a medical condition rather than a moral failing.

And higher education is paying attention. Paul Barreira, an HMS associate professor of psychiatry at McLean Hospital and executive director of Harvard University Health Services, has studied student mental health for many years and has recently looked at how the problem of depression and suicide risk manifests in graduate programs. His reviews have included eight top-tier economics programs in the United States and the Harvard departments of physics and earth and planetary sciences as well as its integrative life sciences programs.

What he found led him to recommend that graduate programs police their own environmental factors that affect students' mental health—and accept responsibility for addressing those factors.

Student health services can help at the individual level but can't handle everything, Barreira says, adding that there is also "an important correlation between the nature of the relationship between students' advising faculty and what their rates are for depression and anxiety." Here, a solution might be to institute a program in which faculty who have a record of working well with students mentor other faculty on how to improve relationships with their advisees.

Interventions being considered in medical education include resilience-based strategies to promote enthusiasm and learning during residency, a focus on student and resident well-being, and encouragement of faculty, peer, family, and social network supports.

While individual-level strategies are worthwhile, there are studies showing that systems-level interventions, such as altering work hours and call schedules, may be more effective, Rotenstein says. This idea is in line with the 2018 *JAMA Charter on Physician Well-Being*, which recommends societal commitments, such as fostering a trustworthy and supportive culture in medicine and advocating for policies that enhance well-being; organizational commitments, such as building supportive systems, developing engaged leadership, and optimizing highly functioning interprofessional teams; and interpersonal and individual commitments, including anticipating and responding to inherent emotional challenges of physician work, prioritizing mental health care, and practicing and promoting self-care.

Mental health is beginning to be more openly discussed and taken seriously as a medical condition rather than a moral failing.

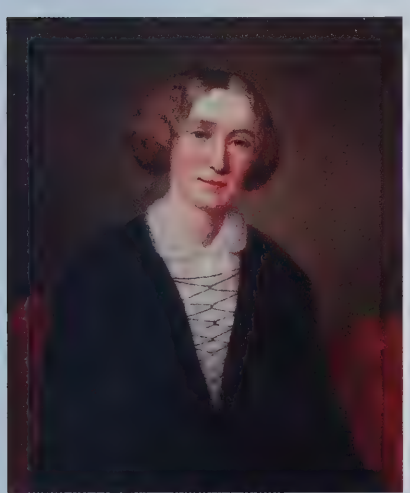
Because of his fears about licensing and residency applications, Morris did not take advantage of the student support structures available when he was an HMS student struggling with depression. He did find the Patient-Doctor 3 course to be a "really profound support network. In it, we all talked about what we were going through as third-year medical students."

Recent School initiatives, says Jennifer Potter, MD '87, an HMS professor of medicine at Beth Israel Deaconess Medical Center, focus on wellness and mental health programs that include structural changes as well as the development of new curricular and extracurricular opportunities.

"Medical school is a challenging experience on many levels," says Potter, who also directs the HMS student wellness initiative and is an advisory dean for students in the Castle Society. "We offer formal and informal instruction in wellness and health promotion approaches such as mindfulness and positive psychology. Also crucial are our programs for students seeking help. We're working to enhance awareness by offering screening for depression; we've expanded counseling hours at student health services, and, through a partnership, we're offering an online counseling service."

Morris and Su each had his own response to their experience with depression, but both are part of a profession that is dedicated to healing. HMS continues to add individual-level programs and infrastructural changes to make the School more welcoming and supportive for all students. HM

Susan Karcz is the associate editor of Harvard Medicine *magazine.*



A recent article in *The Atlantic* presents Tertius Lydgate, the physician in the late nineteenth-century novel *Middlemarch* by George Eliot (left), as an example of physician burnout. Lydgate abandons his early idealism for the conventional trappings of success and ends up disillusioned. Burnout, according to this writer, a radiologist and medical humanities scholar at Indiana University, is not caused by a handful of events but is instead the sum of "thousands of tiny betrayals of purpose."

The Unexpected

BY ANDREA VOLPE

Calls for better screening, care, and treatment for perinatal depression are on the rise—and so are efforts to end the stigma related to the illness

IN THE WEEKS AFTER the birth of her son Owen, Australian writer Jessica Friedmann imagined her suicide: "I would walk out of the house, and cross the highway, leaving no sign behind me. Down the steep hill that led to the river's banks, my hands would reach out for leaves and flowers, touching all the glossy, dew-specked marks of winter growth. Then I would slip out of my clothes, fold them neatly, and disappear beneath the surface of the water."

In *Things That Helped: On Postpartum Depression*, Friedmann writes that knowing that her prior history of depression put her at risk for a recurrence during and after pregnancy, she did everything she could to prepare.

"I see my midwife regularly…alongside the psychiatrist, and together we make plans that are too firm to ever succeed. I will give birth; I will be healthy; I will love my newborn son." Thirty percent of women who, like Friedmann, experienced depression before becoming pregnant risk its return with pregnancy.

Researchers and clinicians increasingly recognize that perinatal mood disorders have their beginnings during pregnancy, not just in the postpartum period.

"The nomenclature in the field has shifted," says Leena Mittal, an HMS instructor in psychiatry, director of the Division of Women's Mental Health at Brigham and Women's Hospital, and associate medical director of the Massachusetts Child Psychiatry Advocacy Program (MCPAP) for Moms. "The term 'perinatal depression,' meaning 'around pregnancy,' fully encompasses depression during pregnancy and the postpartum period, and it can also include people who are struggling with pregnancy loss."

Researchers who study perinatal depression are developing new theories of the disorder, improving our understanding of the variety of causes and symptoms that manifest, and designing new drug therapies. In the clinic, approaches to mental health care during and after pregnancy are beginning to be integrated into prenatal and postnatal care. Improved screening and education, in concert with collaborative models of mental health care for women during pregnancy, are starting to combat what Mittal calls "siloed care models." These efforts are also helping to destigmatize perinatal depression.

Tipping points

The notion that pregnancy is a time of well-being has more to do with cultural mythology than biology. "Pregnancy is not protective from a mental-health standpoint," says Edwin Raffi, an HMS instructor in psychiatry at Massachusetts General Hospital and a member of the MGH Center for Women's Mental Health. It is, he says, a time of stress. "It can be good stress," he notes, "but when you look at that allostatic load, the amount of stress your body can handle, if it goes over a certain threshold, then you're really pushing the nervous system. Pregnancy can be a vulnerable time."

Individuals who experience perinatal depression are a heterogeneous group that includes those who suffer from depression

and become pregnant, those whose depression is in remission and who have a relapse during pregnancy, and those who become depressed for the first time while pregnant. Perinatal depression can occur more than a year after childbirth.

According to a 2018 systematic analysis of more than 200 studies from fifty-six countries published in *Frontiers in Psychiatry*, postpartum depression is the most common complication associated with childbirth, affecting nearly 18 percent of women worldwide. In addition, the analysis showed, countries with higher rates of income inequality and maternal and infant mortality as well as nations where women are more likely to work full-time have higher rates of depression surrounding pregnancy.

Research studies of U.S. populations have estimated that the prevalence of postpartum depressive disorder by state ranges from 8 to 20 percent, with an overall mean prevalence of 11.5 percent. Some of the clinical risk factors found include previous history of depression; pregnancy complications, such as gestational diabetes and preterm delivery; and pregnancy loss. Social factors, including low socioeconomic status, low levels of social or financial support, adolescent pregnancy, and intimate partner violence also were shown to put women at higher risk for perinatal depression.

Untreated maternal depression also places children at risk. "A baby cannot do well if a mother is not doing well," says Mittal.

Postpartum depression is the most common complication associated with childbirth, affecting nearly 18 percent of women worldwide.

Untreated or undertreated depression is associated with pregnancy complications including preeclampsia and preterm birth. A more important risk of depression that goes untreated, adds Mittal, is that it will worsen in the postpartum period and potentially affect mother-infant interactions.

According to some research studies, depressed mothers tend to stop breastfeeding early, and infants of depressed mothers receive less preventive health care. Perinatal depression can manifest in a variety of ways. Mothers might, for instance, be withdrawn from or have more volatile or intrusive engagements with their babies. Such behaviors disrupt parenting and put infants at risk for impaired mother-infant attachment; malnutrition; differences in emotional learning, language acquisition, and social development; and depression that can persist into adolescence.

Alike, yet different

The symptoms of perinatal depression are consistent with those of major depressive disorder, including depressed mood; fatigue; feelings of guilt, inadequacy, helplessness, or hopelessness; and suicidal thoughts. But, Mittal says, for some women "there are very distinct characteristics of perinatal depression."

According to Kimberly Pearson, an HMS assistant professor of psychiatry and a staff psychiatrist at McLean Hospital, perinatal depression "tends to have more anxious or agitated symptoms, as well as intrusive or ruminating thinking."

Some symptoms of depression—disrupted sleep, difficulty with self-care, and loss of appetite, for example—are also often part of the experience of taking care of a newborn.

Clinicians rely on a specialized evaluation tool, the Edinburgh Postnatal Depression Scale, to screen for perinatal depression, Mittal explains, because it can help distinguish symptoms of depression from the physical symptoms associated with pregnancy and the postpartum period. The interview questions in the Edinburgh scale, Mittal explains, are "genius" at zeroing in on perinatal-specific symptoms of depression, particularly self-blame, fear, anxiety, and anhedonia, or the inability to feel pleasure or enjoyment.

Treatment for perinatal depression depends on the timing and severity of symptoms and can involve antidepressant medications, primarily serotonin reuptake inhibitors as well as cognitive behavioral therapy and interpersonal psychotherapy. It can also include helping new mothers and their families cultivate stronger social supports and connections through mom-and-baby therapy or classes.

Perinatal depression is distinct from the baby blues, a period of what Mittal describes as "emotional reactivity," which follows about ten to fourteen days after birth and affects about 75 to 80 percent of women. For the vast majority of women, Pearson says, the baby blues subside after about two weeks, but for some 20 percent of women, feelings of weepiness or of being overwhelmed and

"We're finding that there's a connection between the endocrine system and neurotransmitters that can be a root cause, but this thinking is based on very new studies and very new theories."

JOHN SOARES

anxious can last longer and can evolve into postpartum depression.

There is no single cause of perinatal depression, and research to determine causes is "an active area," says Mittal. "We are still trying to understand the biological underpinnings of the perinatal period and the abrupt changes associated with hormonal flux."

Factor this in

Pregnancy is a complex biological event that affects the entire body. One potential driver of risk that researchers have found, Mittal says, is that the state of hormonal flux associated with pregnancy and with other reproductive hormone-governed conditions such as menarche and perimenopause may put one subset of women at higher risk for depression surrounding pregnancy. Thyroid function, sleep quality, and sleep deprivation may also contribute to mood changes. Genetic factors, such as a personal or family history of perinatal depression, can also contribute.

Recently, researchers have begun to look at how changes in the levels of certain neuroactive chemicals during pregnancy, particularly allopregnanolone, a metabolite of progesterone that rises during pregnancy and falls postpartum, affect neurotransmitters.

"We're finding that there's a connection between the endocrine system and neurotransmitters that can be a root cause," says Raffi, "but this thinking is based on very new studies and very new theories."

Those studies are already providing patients and clinicians with new treatment options. In March, the U.S. Food and Drug Administration approved brexanolone as an intravenous infusion therapy for the treatment of postpartum depression. This is the first therapy developed specifically for this disorder. Three randomized controlled trials of the drug, a synthetic version of allopregnanolone, showed that it improved symptoms demonstrably faster than selective serotonin reuptake inhibitors, the standard treatment to date. The drug's manufacturer recently reported promising results for an oral form of the drug; 45 percent of patients experienced a remission of symptoms after two weeks of treatment.

Systemic influences

Even when reproductive hormones and neurotransmitters are functioning normally, says Raffi, psychological, social, and environmental factors can all contribute to perinatal depression.

Pregnancy is as much a social experience as it is a biological one. It's a time of change and transition, says Mittal, that leads to fluctuations in family structures and interpersonal dynamics. Layer the stress of such changes with genetic, biological, and social vulnerabilities, she adds, and perinatal depression can arise.

"We need to be sure that not just patients, but the people around them, from health care providers to family members, are educated so that we can improve screening, diagnosis, and treatment," says Raffi.

Kimberly Pearson

Pearson would agree: "There's been a big push from the perinatal mental health community to make mental health screening part of obstetric care."

The organization Mittal helps direct is making strides in that direction. MCPAP for Moms was designed to provide perinatal psychiatric consultation and referral to mental health resources for obstetric, primary care, psychiatric, and pediatric providers throughout Massachusetts. An aim of this effort is to build these providers' capacity to identify and manage mental health and substance use disorders in pregnant women through the first year after delivery. The organization recommends screening pregnant women for depression at three time points: during the first prenatal visit; at 26 to 28 weeks; and during the first postpartum visit, which usually occurs four to six weeks after birth.

Massachusetts is the first state to integrate screening for perinatal and maternal depression into prenatal and postpartum care, but initiatives of this type are developing elsewhere. MCPAP is leading efforts to help other states develop similar programs.

Last spring, the American College of Obstetricians and Gynecologists issued new recommendations on postpartum care. Because up to 40 percent of pregnant women do not attend a postpartum visit, ACOG recommended that postpartum care be integrated into prenatal care and that the first postpartum appointment be set for three weeks after delivery. In addition, ACOG recommended that the first postpartum appointment include screening for depression and anxiety.

In February, the U.S. Preventive Services Task Force, citing the short- and long-term negative effects of perinatal depression on mothers and children, the prevalence of the disorder, and the lack of clinical guidelines for its prevention, validated clinical research demonstrating that counseling interventions, such as cognitive behavioral therapy and interpersonal therapy, are effective in helping to prevent perinatal depression. Based on those findings, the task force, which works under the auspices of the U.S. Department of Health and Human Services to make evidence-based recommendations for clinical preventive services, recommended that clinicians provide or refer at-risk women for counseling. Programs cited as models included those that provide group counseling during pregnancy and postpartum and combine cognitive behavioral techniques with psychoeducation, stress management, and education to encourage positive mother-child attachment.

Raffi agrees with the task force's recommendations but calls the guideline to screen high-risk patients "just the tip of the iceberg." There are known risk factors indicating women who have a greater likelihood for developing perinatal depression. Yet despite available effective treatments for the condition, there is not yet a screening tool that can help predict the relationship between risk and developing perinatal depression. At the same time, there is a vital need for more mental health professionals to provide treatment.

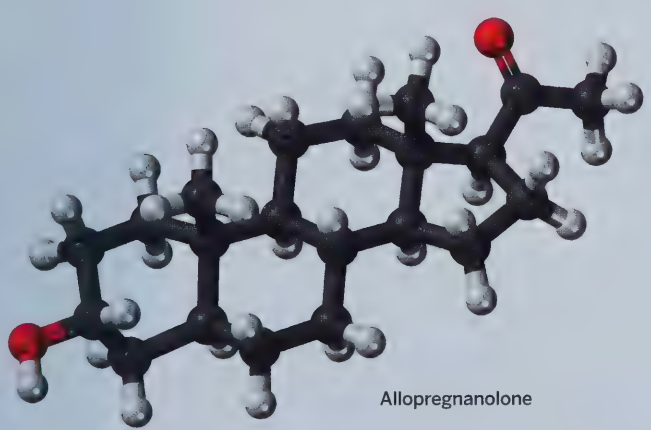
Because up to 40 percent of pregnant women do not attend a postpartum visit, ACOG recommended that postpartum care be integrated into prenatal care.

When it comes to improving screening, education, and treatment, Raffi emphasizes the role of integrated care, from both health care providers and the community. Integrated care can mean having access to obstetricians, prenatal care, pediatricians, and well-baby care as well as social workers and mental health providers all in one place.

It can also mean seeing beyond the mother-child dyad to strengthen support around them. "I think the thing we don't talk about enough is the role of the partner as well as families, employers, and communities in addressing mental health surrounding pregnancy," he says.

"Many times," he adds, "people around us who know us well can help detect changes that are happening to us even before we see or feel them ourselves. A patient's spouse, family, employer, and community can be a great help in detecting a problem and being part of the solution. We spend a lot of time focusing on the mother and the child, but having a child should be a shared experience between the mother and everybody else, so we need to do a better job educating everyone to be active in facilitating care every step of the way. It really does take a village to support a happy family. We should involve the village." HM

Andrea Volpe is a Massachusetts-based writer.



JOHN SOARES

Allopregnanolone

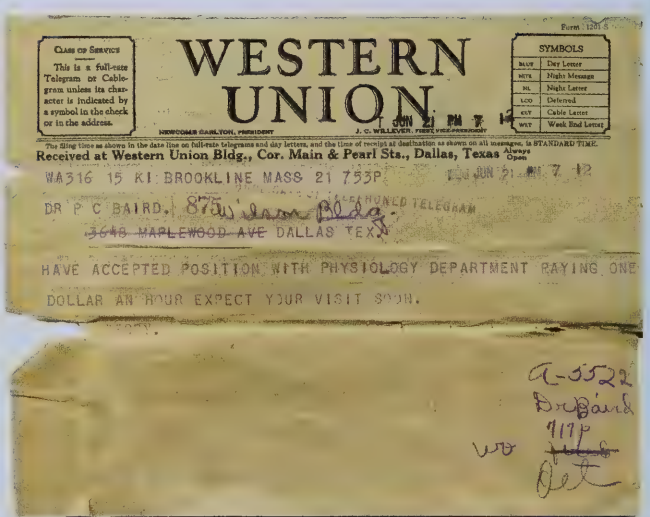
In 1858, French psychiatrist Louis-Victor Marcé published one of the earliest clinical monographs on mental illness during pregnancy and postpartum. In it, he described the return of menses as an important proximate cause: "Of

44 women

suffering from postpartum insanity, who did not nurse, I found

11 (25.0%)

who became mentally ill around the sixth postpartum week, precisely at the time of the return of their menstruation."



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WA316 15 KI BROOKLINE MASS 21 753P

DR P C BAIRD, 875 Wilson Bldg.
~~3646 MAPLEWOOD AVE~~ DALLAS TEX

HAVE ACCEPTED POSITION WITH PHYSIOLOGY DEPARTMENT RAYING ONE DOLLAR AN HOUR EXPECT YOUR VISIT SOON.

A-0522
Dr Baird
917P

Items collected by the family of Perry C. Baird Jr. include a photo of Baird at 18 months (clockwise from top left), two photos of Baird as an HMS student, a June 1926 telegram from Baird to his father announcing his new position in the physiology department at HMS, and a photo of Baird and Gretta, his wife, taken in 1933 in Bala Cynwyd, Pennsylvania.

ALL PHOTOS AND DOCUMENTS COURTESY OF MIMI BAIRD

A manuscript reveals the story of an alumnus whose research on mental illness was cut short by his own

Trouble in Mind

BY PAUL GOLDSMITH

THE STORIES OF LIVES AFFECTED BY MENTAL ILLNESS are often filled with questions, possibilities, and what-ifs. Of myriad futures unexplored. Yet, sometimes there are clues, evidence that can be pieced together and viewed through the lens of time to build a plausible, probable story of what a life might have been.

In the case of Perry Cossart Baird Jr., MD '28, it's easy to imagine what might have been.

"Now, this is an interesting picture," says Mimi Baird, holding a small photo of her father Perry. Mimi, a retired hospital administrator, stands at the kitchen counter of her home in Woodstock, Vermont, hovering over a stack of yellowed clippings and scrapbooks. At 81, she is the guardian of her father's legacy and co-author of *He Wanted the Moon: The Madness and Medical Genius of Dr. Perry Baird, and His Daughter's Quest to Know Him*, a 2015 memoir constructed from a long-lost manuscript handwritten by her father. The manuscript, together with letters and other documents related to Baird's life and work, are housed in the Center for the History of Medicine at the Francis A. Countway Library of Medicine.

"It was taken at Harvard Medical School," she adds. "This is him. You've got the pens in the pocket, the whole outfit." In the photo, Baird wears the fresh whites of a young medical student and faces the camera, his expression flat, dignified, with only a half-smile hinting at his assurance, the certainty he is destined for great things."

"I think Dr. Means saw him taking over the general internal medicine department at the MGH," she says, referring to Massachusetts General Hospital and James Howard Means, MD 1911, a friend and mentor of her father's. "I interviewed somebody out in Texas, and they said he could have been an Everett Koop."

In an alternate timeline, Baird would have had an opportunity to fulfill the almost unlimited potential he flashed as a young researcher and, today, his name might occupy the same place of honor as the medical and scientific men who trained, mentored, and groomed him for success—Means, Fuller Albright, MD '24, and Walter Bradford Cannon, MD 1900.

Perry and Gretta's daughters Catherine (Kitsy, left) and Mary Stewart (Mimi) pose for a photo taken in 1942.

The Perry Baird known to many of his contemporaries was a handsome, fashionable man of privilege, tall and broad, confident in his talents and abilities; a successful dermatologist in the Boston area with a thriving practice in a building on Commonwealth Avenue; a well-dressed charmer who belonged to The Country Club in Brookline and the Norfolk Hunt Club, where he owned three horses; a regular at the Ritz and the Satire Room, the jazz lounge at the Hotel Fensgate. Cutting an erratic trail through Boston Brahmin high society, Baird was a character out of an F. Scott Fitzgerald novel. But like the greatest of Fitzgerald's characters, Baird's gifts were tempered with darkness and, ultimately, tragedy.

In 1934, Baird set out to do something many in the medical establishment deemed not only improbable, but impossible—provide biological evidence that psychiatric disease was a physiological rather than a psychological condition. His search would cost him his reputation, his career, his family, and his freedom. But his story is not solely about what was lost.

Shooting star

Growing up in Mexia, Texas, a small town on the Navasota River south of Dallas, Baird was an energetic, confident child, devoted to academics. He arrived in Boston in September 1924 to attend HMS. In his first year, he began working in the physiology lab of Alexander Forbes, MD 1910, and he distinguished himself as a dogged research scientist. By the end of his third year, Baird had co-authored three papers, all published in the *American Journal of Physiology*.

His intelligence and enthusiasm earned the attention of Forbes' mentor, Cannon, the chair of the School's Department of Physiology. At that time, Cannon was at the height of his influence and scientific fame. In him, Baird found more than a mentor; he found a role model.

Baird graduated at the top of his class at HMS and completed his internship at University Hospital in Ann Arbor, Michigan. In 1930, he returned to Boston to begin his residency at Mass General, intent on following in Cannon's footsteps.

But Cannon and Means had other plans. They thought Baird the perfect candidate to bring dermatology at Mass General into the modern age and arranged for him to begin a one-year residency under John H. Stokes, a noted expert in dermatology and syphilology at the University of Pennsylvania in Philadelphia. Before completing that residency, however, Baird traveled to Buffalo at the request of Albright, himself a rising star in the burgeoning field of endocrinology, to observe a new medical procedure for treating patients with Addison's disease, a life-threatening condition in which the adrenal glands fail to produce sufficient amounts of cortisol and aldosterone. Upon his arrival in Buffalo, Baird

wrote to his parents: "a Dr. Hartman has developed a process by which a substance can be extracted from animal glands and used to keep these patients alive indefinitely. Three of these patients were dying under our eyes. Extract was shipped to us. We injected it. The dying came back to life and to health. Dr. Hartman can supply us only for six weeks. After that, we must make our own 'Cortin.' I have been sent to Buffalo to learn the process. It will require ten days to two weeks. I expect to be working day and night."

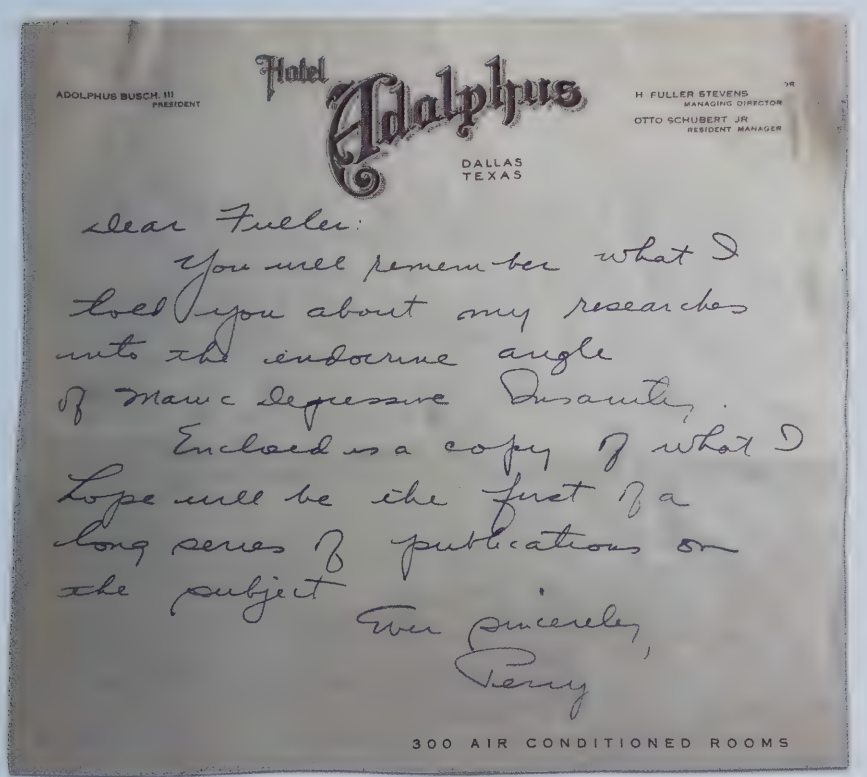
Together, Baird and Albright began work on a paper detailing this new treatment and the role of the adrenal cortex in the production of corticosteroids. In the fall of 1932, Baird, now living in Philadelphia, sent Albright an early draft of the paper. Albright responded with a detailed list of edits. The edits sparked two dense replies from Baird, each crackling with energy: "Send me that curve on the effect of pituitrin, and I will send you my I.O.U. for six bottles of champagne."

Days later, Means found Baird wandering the streets of New York City in the midst of a severe manic episode. Recognizing Baird's distress, Means arranged for him to be transported to Philadelphia, where he was admitted to the Pennsylvania Hospital for Mental and Nervous Disorders.

Baird was 29 years old when he was admitted to the hospital in December 1932. Diagnosed with manic depressive psychosis, today known as bipolar disorder, he spent much of his hospitalization in a medically induced coma. When he emerged after 25 days, he found the course of his life had been permanently altered.

The episode cost Baird his fellowship, and his chance at becoming a professor of dermatology at HMS. But it didn't cost him his mentors. Means and Cannon offered their support, suggesting he move back to Boston and open a private practice. Baird accepted the advice and, along with his new wife, Gretta, returned to Boston to begin a life as a private practitioner.

When he emerged after 25 days, he found the course of his life had been permanently altered.



In 1942, Baird wrote Fuller Albright, his collaborator on research on the role of the adrenal cortex in the production of corticosteroids, to solicit his comments on Baird's manuscript for "Biochemical Component of the Manic-Depressive Psychosis."

Underneath, he remained a man on fire, full of questions and ready to seek answers.

The state of the art

The idea that mental illness is biological in nature, as opposed to simply imagined or invented, wasn't new. In fact, at the turn of the twentieth century, it was the prevailing notion. Prominent clinicians such as the German psychiatrist Emil Kraepelin—who coined the term manic depressive insanity—theorized that mental illness was a form of intoxication, or "self-poisoning," caused by either an excess or lack of some naturally occurring biological substance. Despite broad agreement on the merits of this theory, scientists were unable to provide empirical evidence to back it up. Adolf Meyer, the first psychiatrist-in-chief at Johns Hopkins, wrote: "As long as chemistry can not [*sic*] furnish more accurate data and methods, the theory of intoxication and autointoxication so often resorted to by Kraepelin will be a *terminus technicus* for our ignorance."

Lacking a solid scientific foundation, the autointoxication theory stalled, gradually ceding ground to another emerging school of thought. By the 1920s, psychoanalysis, which posits that mental illness is the result of unconscious conflicts or repressed memories, was on its way to becoming the dominant force in clinical psychiatry in the United States.

Baird, with his diagnosis of manic depressive illness, entered a world in which

psychoanalysis reigned. From his doctors and colleagues to his friends and family, the consensus was that Baird's problems were not only of his own making but also in his hands to control.

In the manuscript that became *He Wanted the Moon*, Baird captured some of these character assessments. "All Perry's troubles are sexual," he overheard one physician colleague say. According to his psychiatrist, Baird's manic episodes would be controllable provided he stay away from whiskey. And a hospital psychiatrist offered him this advice: "live a regular life, eat and sleep regularly. Have sexual intercourse about three times per week. Reduce your income to $15,000 per year. Don't overwork. When you feel yourself getting manic, just don't talk so much."

But Baird was an empiricist, a physiologist. He rejected the abstractions of psychoanalysis, believing there had to be a biological explanation for his psychosis. In 1933, shortly after his release from his first hospitalization, Baird wrote to Cecil Drinker, a physiologist and former dean of what was then the Harvard School of Public Health:

"Analytical and synthetic thinking of a physiological variety is surely one of the great delights of living. The one thing which I most love to do is physiological research of a nature which is open to procedures which can be carefully controlled. More specifically speaking, I cannot suppress my burning desire to continue my studies of the relationship between the anterior pituitary gland and the adrenal cortex. I am convinced that such research would yield a steady harvest of interesting data."

Baird's scientific mind was busy connecting dots. Drawing on his work with Albright, as well as earlier work by Cannon that described the role of adrenaline in states of intense emotion, Baird hypothesized that a malfunctioning adrenal cortex might be to blame for his condition.

Baird's scientific mind was busy connecting the dots.

On a mission

At the same time he was settling into his new life as a practicing dermatologist, Baird was using a laboratory provided by Cannon to conduct an observational experiment to test his theory. Employing a technique pioneered by Cannon, Baird surgically removed the adrenal glands of twenty cats, then separated the animals into two groups. One group received abdominal injections of blood drawn from patients with mania at McLean Hospital; the other group, the control, received blood from healthy individuals.

By the end of the experiment, the animals that received blood from patients with mania had lived 40 percent longer than those in the control group. Although the reason for this was unclear, and did not provide him the insight he'd hoped for, it was enough to convince him he was on to something.

On November 3, 1934, Baird wrote to Cannon asking permission to continue his experiments: "We would carry on with our effort to determine whether or not it can be demonstrated biologically that the blood of a patient in a manic state can be distinguished from a normal blood similarly tested."

Eight days later, Baird was admitted to McLean. He was, he wrote, "over-active, euphoric and excited." According to hospital records, he became violent, smashing furniture and windows, and threatening staff. He was released a month later.

In a letter penned shortly after Baird's release, Cannon wrote: "Everybody has a critical stress which he can stand. … The prudent person is one who learns by careful observation where that stress lies and manages his life so that he lives within the limits." At the urging of Cannon and Means, Baird agreed to abandon his research into the cause of manic depression.

He again settled into domestic life with Gretta. They became the parents of two daughters, Mary Stewart (Mimi) and Catherine (Kitsy). Baird's practice thrived, thanks in part to the steady stream of patients referred to him by Cannon, Means, and others.

Yet Baird still wanted answers. He succeeded in again enlisting the support of Cannon, Means, and Kenneth Tillotson, then psychiatrist-in-chief at McLean. In 1940, he resumed his research; by the spring of 1942, he had completed a paper reporting his findings.

The vortex of his disease, however, proved inescapable. In early May 1942, he was readmitted to the Pennsylvania Hospital for Mental and Nervous Disorders. He escaped days later.

Over the next year, as Baird polished his article for submission, he was hospitalized five more times, the fifth time in February 1944 in the Westborough State Hospital in Massachusetts.

"Perhaps this report will stimulate added interest in the manic psychosis as a physiological and general medical problem rather than as a purely psychological one. It may be hoped that other investigators will continue these studies."

The paper that had haunted Baird for a decade came out two months later in the *Journal of Nervous & Mental Disease* while he was still hospitalized at Westborough. Around the same time, Gretta filed for divorce. Shortly after, he received word that his medical license had been revoked.

While earlier drafts of Baird's paper included Cannon and Tillotson as co-authors, the final published version lists only Baird. As with his earlier experiment, his results were promising but inconclusive. In the paper, Baird suggests the study is best viewed as proof of concept, a justification for deeper inquiry, and a reluctant recognition of personal limitations:

"This paper is preliminary in nature but is published at this time because of the necessity of postponing further experimentation for an indefinite and uncertain amount of time. Perhaps this report will stimulate added interest in the manic psychosis as a physiological and general medical problem rather than as a purely psychological one. It may be hoped that other investigators will continue these studies."

Baird had once hoped to complete a series of papers on manic psychosis, but even his calls for continued study went unanswered. "Biochemical Component of the Manic-Depressive Psychosis" would be cited only five times, the last in 1952.

Lonely are the brave

It's difficult to point to a single reason why Baird's study went largely unrecognized. As *He Wanted the Moon* points out, the paper came out at the height of World War II, when many of Baird's colleagues were overseas. Baird may also have been the victim of bias, based on the stigma of his own particular mental illness.

"Bipolar, at the time, was very much the neglected psychosis," says Anne Harrington, the Franklin L. Ford Professor of the History of Science at Harvard and the author of *Mind Fixers: Psychiatry's Troubled Search for the Biology of Mental Illness*. "In contrast to schizophrenic patients, who were often seen as pliable lost souls, there was often less interest in working with bipolar patients, because they tended to be viewed as both very smart and manipulative."

There are indications that Baird's colleagues took the view that his research was just a complicated way of rejecting his own responsibility for the havoc he wreaked. Today, some think Baird's thinking was simply ahead of its time.

"I suspect his ideas were too far out there for the 1940s," says Ross Baldessarini, an HMS professor of psychiatry who founded and directs the International Consortium for Bipolar & Psychotic Disorders Research at McLean. Baldessarini is one of a handful of researchers of bipolar disorders who have rediscovered Baird's work, thanks in part to the efforts of Mimi Baird and the publication of *He Wanted the Moon*.

In Baldessarini's view, Baird was a pioneer in looking for objective evidence, even if his work failed to yield any clear-cut explanations for the cause of a major mental illness.

"He was no worse off in that regard than we are today because we still don't know," Balsessarini adds.

In his quest to find a biochemical cause for bipolar disorder, Baird was seeking understanding. In this way, his paper has more in common with modern approaches like psychiatric genetics, which tend to focus on pathogenesis and the identification of biomarkers, than with the psychoanalysis-heavy publications of his time.

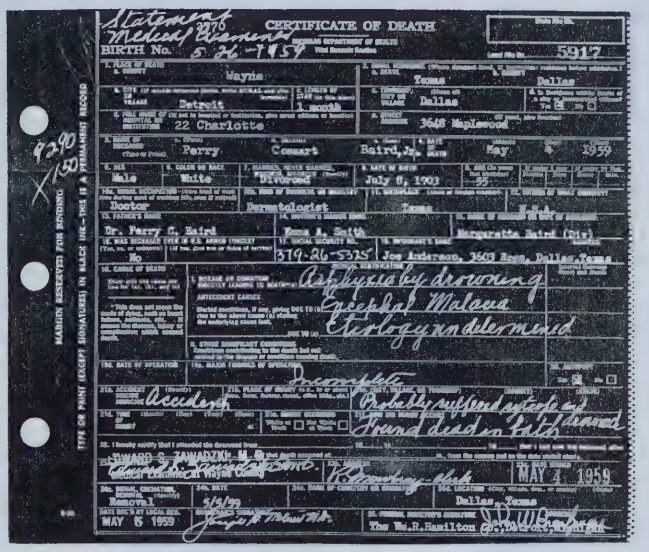
"This is a case of somebody who is looking for a cause, not a cure, and that's important to note," says K. Sue O'Shea, director of the University of Michigan Center for Pluripotent Stem Cell Research.

"He wasn't trying to alleviate suffering in the short term," she adds. "He was attempting to shift the paradigm in psychiatry with testable hypotheses. You really need to understand the biochemical basis of the disease to develop rational treatments."

As part of her research, O'Shea is using stem cells derived from patients with bipolar illness to model the disease in living tissue.

Proof of concept

There is one final turn to Baird's story, one that adds poignancy and a sense of what biomedicine lost to his illness.


Statement of Medical Diagnosis
CERTIFICATE OF DEATH
BIRTH No. 5-24-1959
5917
Wayne
Detroit
1 month
Texas
Dallas
Dallas
22 Charlotte
3648 Maplewood
Perry
Conant
Baird, Jr.
May 1959
Male
White
Divorced
July 8, 1903
55
Doctor
Dermatologist
Texas
Dr. Perry C. Baird
Rena A. Smith
Margarette Baird (Sis)
No
519-26-5325
Joe Anderson, 3603 Rose, Dallas, Texas
Asphyxia by drowning
Cerebral Malaria
Etiology undetermined
Accident
Probably suffered attack of Malaria
Found dead in bath tub
EDWARD S. ZAWADZKI, M.D.
MAY 4 1959
4/5/59
Dallas, Texas
MAY 5 1959
The Wm. R. Hamilton Co.
MARION RESERVED FOR RECORDS
TYPE OR PRINT (EXCEPT SIGNATURES) IN BLACK INK—THIS IS A PERMANENT RECORD

Baird's death certificate was issued in 1959 by the medical examiner of Wayne County, Michigan.

Four years after Baird's paper and half a world away, John Cade, a 37-year-old psychiatrist and former prisoner of war working at the Bundoora Repatriation Mental Hospital outside of Melbourne, had an idea that the blood chemistry of his patients with mania might differ from that of healthy participants. Using a converted kitchen as a lab, Cade, unaware of Baird's research, tested his hypothesis by injecting blood and urine from patients with manic disorders into guinea pigs.

When results indicated that the procedure caused toxic levels of uric acid, Cade added lithium salts to his solution as a dissolving agent. To his surprise, the lithium solution had a visibly soothing effect on the animals. That moment of serendipity led to one of the more significant pharmacological breakthroughs of the twentieth century—the discovery of lithium carbonate for the treatment of bipolar disorder.

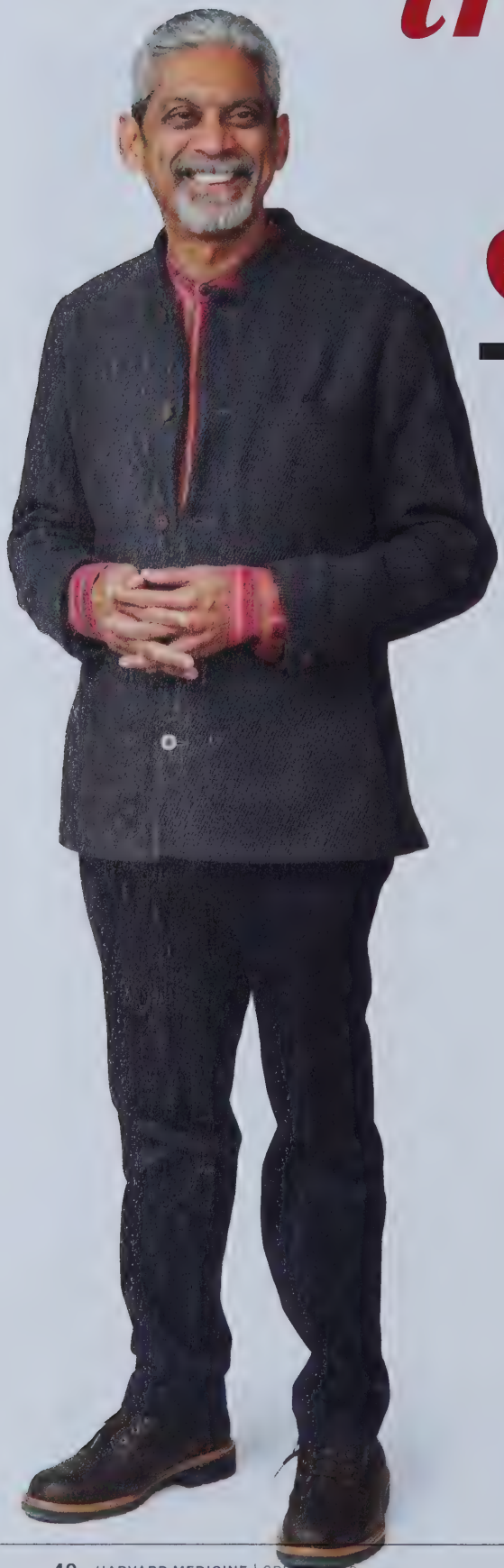
Cade's breakthrough arrived too late to save Baird. In September 1949, when Cade published his findings in *The Medical Journal of Australia*, Baird was confined to the State Psychopathic Hospital in Galveston, Texas, awaiting a prefrontal lobotomy. After the surgery, Baird lived with his parents and brother in Texas before moving to Detroit in 1959 to take a job as an ambulance attendant. He died on May 4, 1959, following a seizure in the bathtub of his boarding house.

Cade would go on to be celebrated as one of the pioneers of modern psychiatry, while Baird slipped quietly from history.

Paul Goldsmith is a Boston-based writer.

in 5

A conversation with Vikram Patel, Pershing Square Professor of Global Health, Department of Global Health and Social Medicine in the Blavatnik Institute at HMS and professor, Department of Global Health and Population, Harvard T.H. Chan School of Public Health



JOHN SOARES

You are an advocate for global mental health equality. Where does this passion stem from?

As a medical student, I was interested in neurology. I was fascinated by the brain and diseases of the brain. However, I found neurology rounds disappointing. The focus seemed to be almost entirely on the art of diagnosis. Once a diagnosis was made, there seemed to be little further interest in the person or their suffering. I found this to be disheartening. In psychiatry, by contrast, the first questions a consultant would ask a patient were about their personal circumstances such as, who do you live with? and what do you do for a living? I found psychiatry to be a more humane, more person-centered, more dignified, and more interesting way to approach problems of brain health.

If you could change one thing about our understanding of mental health today, what would it be?

The idea that mental health care is the domain of mental health specialists only is one that I would like to see revoked altogether. Mental health is important to each and every one of us, and we all need to be equipped early on with skills and knowledge of how to protect and promote our mental health and how to deal with mental health problems. Mental health is everyone's business.

What developments are poised to transform mental health globally?

One innovation that has been demonstrated and is becoming increasingly mainstream is that anyone who is sufficiently trained and supervised to deliver a specific mental health intervention can be a mental health-care provider. Another is the use of digital technologies in almost every aspect of mental health care—from prevention and promotion through treatment and recovery. A third is the increasing convergence between our understanding of the functions of brain circuits and networks with psychological interventions designed to target these brain circuits and networks. I foresee the real prospect of neuroscience, psychological science, and clinical science converging, something I don't think we could have even imagined a decade ago.

What is the most dramatic change in the field of mental health you have witnessed in your lifetime?

The acceptance of mental health problems as universal forms of human suffering that have been described in very similar ways across cultures, across societies, and importantly, across time. Different cultures and different societies have evolved different ways of dealing with mental health problems, but there are surprising similarities across the approaches used. The belief that the nature and care of mental health problems is highly culture specific was once a dominant idea. Today, I think we know this is not the case.

Good mental health is impossible without ...

Good mental health is impossible without recognizing its central value in your life.

—Ekaterina Pesheva

Advocacy for the humane care of people with mental illness set the stage for better conditions, more medically based approaches

In the nineteenth century, public institutions known as almshouses housed the homeless, aged, ill, destitute, and criminal, along with the "insane" or "feebleminded." And all too often, the conditions in these shelters gave cold comfort.

Citizens horrified by what they saw while visiting these institutions began to take up the cause of improving conditions for the residents of almshouses, particularly the mentally ill. L. Vernon Briggs, a Boston psychiatrist, and Dorothea Dix, the social reformer, were two of these champions of human dignity.

Briggs, an advocate for the imprisoned as well as for the mentally ill, campaigned for transparency in the Massachusetts asylum system and for more funding and more oversight in hiring physicians and staff. In 1914, he was appointed to the Massachusetts State Board of Insanity. Writing in *The Medical Review* that same year, Briggs abhorred not only how people with mental illness were forced to live but even the way they were spoken of. He felt the "temptation to eliminate the word 'insane,' … as it really conveys no more idea of the condition of our mentally ill than does the word fever convey to us any particular form of disease."

Briggs practiced in Boston for some fifty years and worked closely with the like-minded "alienist" Walter Channing, MD 1872. Their collaboration on Channing's private sanatorium in Brookline, Massachusetts, allowed Channing to put his own ideas of proper and humane treatment of mental illnesses into practice.

Dix, working a generation earlier, laid the groundwork for Briggs's work by raising awareness among the public and lawmakers about the cruel treatment of people in asylums. She founded or improved more than thirty of these institutions, and was, for most of her adult life, an advocate for the humane treatment of people with mental illness. —*Susan Karcz*

Early twentieth-century images from the collection of L. Vernon Briggs show interior and exterior views of what is described as Maryland's "Worcester County, Alms House … Bldg. for Negroes, Men and Women in same Building."

Student Life

Edith Gahleitner

THROUGHOUT HER LIFE, EDITH GAHLEITNER has been sensitive to the plight of individuals who were displaced, dismissed, or otherwise marginalized by economic, social, or political circumstance. Although she followed her love of sculpturing early in life, the turmoil in the world—the Arab Spring in 2010 and the Syrian crisis, for example—prompted her to redirect her talents. She turned from fine art to the study of medicine, pursuing her medical education and training in Canada, Europe, India, and Israel. Her focus throughout her studies: ways to provide contextually and culturally sensitive mental health care for people who have been displaced by conflict and have experienced violence.

Gahleitner is now a psychiatry resident in Switzerland and recently became a first-year student in the HMS Master of Medical Sciences in Global Health Delivery program.

Gahleitner began her residency training in gynecology and obstetrics in Switzerland, where she treated women from areas of conflict. All had survived sexual and gender-based violence. The experience prompted her to seek out more training in psychiatry and psychotherapy.

"To help a woman heal, I felt I could do better by integrating psychiatry with psychotherapy, by taking an integrated psychosocial approach," Gahleitner says.

While pursuing her education at HMS, Gahleitner continues to work for a nongovernmental organization in Germany, providing training for health professionals caring for refugees, with a special focus on working with women and girls who have experienced sexual and gender-based violence. The trainings also emphasize the importance of caregivers tending to one another.

"I think if you're part of an organization providing care for a vulnerable group of people, it's important to also take care of the people who are providing that care," Gahleitner says.

During her tenure at HMS, Gahleitner plans to use a human-rights approach to investigate the intersection of psychiatry and child protection issues. She intends to research the consequences of immigration policies and practices; distress migration, that is, migration triggered by a complex set of circumstances including natural calamities and a lack of economic options; and humanitarian assistance on the psychosocial and mental health of child and adolescent refugees.

Gahleitner thinks that being a clinician, a researcher, and a teacher provides her with a firm foundation for speaking out against human rights violations. She would like to see physicians amplify their voices to urge politicians to provide funding for care and to change immigration policies.

—Bobbie Collins

Chenjezo Grant Gonani

AT FIRST, CHENJEZO GRANT GONANI had a hard time believing that his friend was sick. He had just spoken with him, and everything had seemed fine. But when Gonani visited one night, the family had locked his friend in his room and wouldn't let him out. They said he'd been running around, shouting, and smashing windows.

"To me it was shocking," recalls Gonani, a second-year student in the HMS Master of Medical Sciences in Global Health Delivery program. "He'd be fine, then he'd be manic."

Gonani, who was then working as a general practitioner for the Malawi Ministry of Health, recognized that his friend likely had bipolar disorder. In their search for treatment for the man, his family was consulting various traditional and faith healers, not the staff at a nearby district hospital.

Yet, as the disorder worsened, the family worried that they couldn't keep him safe or protect others from his outbursts. They took him to the hospital where the staff, ill-prepared to deal with serious mental illness, put the man in chains and transferred him to the mental health hospital in the capital.

In Malawi, a nation of 19 million in southeastern Africa, many people view mental illness as a spiritual issue, a malady not trusted to staff at district hospitals. According to Gonani, in Malawi 80 percent of patients with mental health illness are untreated and live with their families.

"We have to build services that will work within the complex cultural, social, and economic context of the community," he says.

To contribute to this change, Gonani enrolled in a degree program in mental health care at Malawi's St. John of God College of Health Sciences, and, following graduation, he established a mental health clinic in the district hospital in Neno and began traveling to the district's other community health centers and making visits to patients' homes.

He also attended the Harvard Global Health Delivery Intensive Program, a bootstrapping course for delivery science, where he learned how to train general practitioners and community health workers to identify people with mental health illnesses, refer them for treatment, and provide them with basic support services.

In his master's program at HMS, Gonani is gaining skills that he will take to Malawi to help achieve his goal of developing care networks for people with mental illnesses that involve families and traditional community leaders.

"You have to dig down to try to understand the cultural context before you build," Gonani says. "You have to understand things from the inside out."

—Jake Miller

Miao Xue

THE FIRST THING THAT ATTRACTED Miao Xue to the study of psychology was a deep curiosity about people's inner worlds. She liked the idea that studying the mind would reveal important truths about the human condition.

The pursuit of that study has taken Xue, a first-year student in the HMS Master of Medical Sciences in Global Health Delivery program, on journeys far from her home in Beijing, China. These travels have allowed her to explore the social and cultural aspects of self—and of mental health.

When Xue graduated from high school, she says, a shortage of opportunities to study psychology in China led her to a program in Poland.

Living within another culture allowed Xue to see her own anew. In China, as elsewhere, mental health isn't just about mental illness or an individual patient's mind, she realized. It's about an interlocking set of factors that includes biology, culture, politics, and social interactions.

In addition to her work as a psychologist in a psychiatric hospital in China, she began developing a support program for the families of the mentally ill.

"If you only talk about the person as a patient, it's too narrow a vision," Xue says.

Social and economic support for family members who are caring for mentally ill loved ones may also be part of a comprehensive solution of treatment and support, Xue says. In China, she notes, mental illness can impoverish a family if it means losing the incomes of both the person who is ill and their caregiver.

For her master's program research project, Xue is developing an intervention to promote the well-being of families, particularly children, who are living with parents with mental illness.

While in Boston, Xue continues to bring together the viewpoints of different cultures by mining the perspectives of scholars at Harvard's Kennedy and divinity schools and considering how those perspectives can contribute to global health equity programs. Xue hopes that these insights, along with data she will collect from surveys, will help her develop better programs in China for parents with mental illness—programs that help them heal, help support family members who serve as caregivers, and prevent their children from suffering undue trauma, such as separation or the feeling that they are to blame for their parent's illness.

"There are so many brilliant ideas about how to help," Xue says, "but there's a big gap between having those brilliant ideas and delivering the care that people need."

—Jake Miller

In Service to a **Nation**

ROGER MONTGOMERY WILL TELL YOU he has not done anything that special. Talk with him awhile, and you will learn otherwise.

Montgomery, a member of the Cherokee Nation and a self-proclaimed "Okie from Muskogee," says he has come full circle in his professional odyssey. After finishing his residency at Boston City Hospital, he moved to Oklahoma to work at an Indian Health Service hospital, then to a traditional primary care practice. Now, Montgomery is the executive medical director of Cherokee Nation Health Services. This professional journey was not an easy one, but it was necessary: Montgomery wanted to serve the Cherokee community.

It was a high school science teacher who first planted the idea of becoming a physician in Montgomery's young mind. The idea flourished, but slowly.

"It took several years of being a doctor before I realized that I was suited to be a doctor," he says. "I'm forever indebted to this wonderful teacher, who challenged and nurtured me along the way." The two remain friends to this day.

Montgomery wanted to attend the University of Oklahoma College of Medicine, but Willard Mounce, a Cherokee citizen who was also an HMS student, had other plans for his friend. He not only encouraged the reluctant Montgomery to apply to HMS, he sent him the application and funds to cover the application fee. When Oglesby Paul, MD '42, then director of admissions at HMS, called and invited Montgomery to Boston, he did travel east, albeit, he says, "under duress."

Making the transition to medical school and Boston brought its challenges. Fortunately, Montgomery again found encouragement from someone who would become a mentor: Daniel Federman, MD '53, then dean for students at HMS. Montgomery recalls talking with Federman about whether he, coming from rural Oklahoma, "belonged" at HMS. Federman, says Montgomery, was the "kind of person you could talk to, someone who never acted as if belonging was even an issue."

Cherokee Nation Health Services is the largest tribal health service in the country, and although Montgomery's role is more administrative than clinical, he's grateful for the opportunity to help improve the health of tribal members. One standout project aims to eradicate hepatitis C in the tribal community.

He is also excited about his involvement in a new medical school, projected to open in 2020, that represents a collaboration between Cherokee Health and Oklahoma State University. The school will be the first tribally affiliated medical school in the United States. Montgomery and others hope its graduates will help alleviate the shortage of primary care physicians in rural Oklahoma. With work that addresses the near- and long-term needs of the Cherokee people, Montgomery remains dedicated to improving the health care system that serves them and, in the process, is helping future generations flourish.

—Susan Karcz

Roger Montgomery, MD '85 | Executive Medical Director | Cherokee Nation Health Services

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DO NOT WRITE BELOW THIS LINE

Reading List

The influence of a skilled and thoughtful mentor never wanes

BY EDWARD HUNDERT

During his decades-long career at HMS, Leston Havens mentored generations of medical students.

PHOTO COURTESY OF SUSAN MILLER-HAVENS

IN THE MID-1950S, Leston Havens, psychiatrist, professor, author, patient advocate, and, for me, a mentor extraordinaire, began a residency at what would become Massachusetts Mental Health Center. During his nearly three decades at the center, Les helped define the fledgling field of biological psychiatry, including founding the center's psychopharmacology unit, serving as chief psychiatric consultant to the Massachusetts Rehabilitation Commission, and directing the medical student clerkship, where he introduced generations of medical students to psychiatry as a career. Later, during his appointment at Cambridge Hospital, Les directed its psychiatry residency for many years.

His academic career was centered at HMS, where, in 1954, he began as a teaching fellow in psychiatry and, by 1971, earned the rank of full professor. In 2008, he became a professor emeritus of Harvard University. Havens died in 2011.

Threaded throughout these many legacies is the legion of psychiatrists who, as medical students, took a month-long one-on-one elective that we called Reading with Les. It was an experience that not only dramatically influenced my understanding of the history of psychiatry, but also led to almost ten years of monthly faculty club lunches during which Les would encourage me, prod me, and always leave me with the feeling that I could accomplish so much more than I ever thought possible.

I learned about his reading elective from a fellow student as we were waiting for a conference to begin. Les was coming to interview a patient from whom none of the residents or students could get even a basic history: the woman's experience was completely filled with terrifying hallucinations. Les entered, pulled his chair up next to hers, and within a few minutes, to the astonishment and awe of the students and residents in the room, proceeded to have about a half-hour long, rather normal conversation about who she was and her life. I still remember how she talked with him about her work as a clerk at the MIT Coop and her memory of selling the last slide rule in inventory. Calculators were coming in.

Afterward, Les took questions. A resident asked why he thought that patients who hear voices so often think it's the voice of God that they hear. He paused, then said, "You know, there are lots of kinds of suffering. Physical pain, for example. But the kind of suffering our patients experience really is the worst kind of human suffering, and God doesn't talk to just anyone." He left it there.

When next I spotted him on the ward, I raced over and asked if I could sign up for one of his reading months. He said he would look forward to it and later let me know that I should read in advance the book we would discuss at our first session: Karl Jaspers's *General Psychopathology*. After we discussed Jaspers for what turned out to be two hours, he assigned me John William Miller's *In Defense of the Psychological*, which affected my thinking more than any single book I'd ever read.

These meetings with Les were like classic Oxford tutorials: the wise tutor listens to his young charge discuss the last reading assignment, then chooses the next reading assignment based both on an appreciation of the student's ongoing misconceptions and an insight into which texts will best challenge the student's growth to the next level of understanding.

It was during our discussion of *In Defense of the Psychological* that I confided to Les that I had a contract with Oxford University Press to write a book on various approaches to the mind. He replied, "Well, in that case, next week we should discuss a little effort I cobbled together with that same title about ten years ago."

We moved on to his *Approaches to the Mind*—and my life was changed.

When I was in college, I had a double major in math and the history of science and medicine. I thought I had some understanding of the way the history of science and medicine unfolded. In science, the paradigm is always physics, chemistry, or biology, where the Kuhnian revolutions of deeper levels of understanding don't merely build upon but ultimately replace the older ones. Newtonian physics supplanted both Aristotelian physics and Ptolemaic epicycles, Einstein supplanted Newton, and so on.

That linear view is usually what medical students are taught, too. Darwin's theories make so many others obsolete, and the discovery and study of bacteria or DNA relegates previous theories about black bile and other humors to history books instead of medical books.

But Les didn't see the history of psychiatry that way. He believed, and taught, that each school of psychiatry—psychodynamic psychiatry, biological psychiatry, interpersonal psychiatry, existential psychiatry, and so on—brings a different and complementary truth to the table. One does not supplant the next. Instead, each uncovers different sets of fact that should never be understood as contradictory.

In psychiatry, he once wrote, "There can be no separation of facts and methods. Each fact is secured by a particular limited method, and each method is scientific only insofar as it secures consistent facts." Then he added, "These points should not be overlooked if one hopes to grasp the whole universe of mental phenomena with a few methods and facts."

I think Les was a master teacher in part because he had a deep understanding that no one school of psychiatry represents an all-inclusive method for understanding mental phenomena. In the introduction to his *Approaches to the Mind*, Les talked about how each school of psychiatry is convinced it is *the* psychiatry: "Students shop among the schools, and the public asks psychiatrists and psychologists what *kinds* they are ... new varieties come and go like fashion styles." Beginning students can feel they are, as he put it, "prisoners of a point of view."

While some people interpret this viewpoint as nihilistic, Les didn't intend it that way. Indeed, he devoted all his remarkable powers to celebrating the plurality of perspectives and tools that each psychiatric school brings to bear. Elsewhere in the introduction to *Approaches*, he wrote, "Many of us enter psychiatry and psychology seeking a bridge between science and the arts, a unity of knowledge and experience ... certainly not their fragmentation. We wanted to carry all our life's experience, as well as the intuitions and colors of art, over into science and the practice of therapy."

Then appears one of my favorite sentences among the millions he wrote: "We wanted to be as much whole persons in our professional lives as elsewhere, to have each part serve every other part, whether personal, social, or professional."

Most people don't know that Les did a residency in internal medicine to prepare himself for studying the relationship between mind and body.

This integrative view of the history of psychiatry is indeed more like the history of art than the history of science. Yet it's important to recognize that the conclusion that Les reached was not that psychiatrists should be what is often described as eclectic: "... the psychiatrist or psychologist does not want to be merely eclectic, that is, borrowing whatever pleases him from various sources. He wants to be *pluralistic*, able to use all the methods and make the critical observations himself, and to be capable of grasping when and with whom each method should be applied." Only in this way, he said, can we speak of an inclusive or pluralistic psychiatry, concluding that "having painted our portrait from more than one angle, we may be closer to objectivity."

Most people don't make the connection that Les was interested in getting closer to objectivity, instead thinking of him as the guru of clinical work, as someone deeply interested in the phenomenology of mental life and mental illness, as someone who was able to align his subjectivity with the inner life of the patient and make contact with them in a way few other people could.

What most people also don't know is that he did a residency in internal medicine to prepare himself for studying the relationship between mind and body. Furthermore, many of his awards were for biological research. The first award he ever received was for diagnosing a patient who was considered psychotic as having liver disease instead. Les proved that the patient had elevated blood ammonia levels and that it was his liver, not his psyche, that needed medical attention.

The subtitle of *Approaches to the Mind* is *Movement of the Psychiatric Schools from Sects Toward Science*. According to Les, that movement did not follow the scientific historical trajectory in which inferior theories are disproven as we move closer to objectivity. He taught us that the way we move closer to objectivity, the way we can be scientific in psychiatry, is to embrace seemingly contradictory theories and become pluralistic psychiatrists who can paint patients' portraits from multiple angles at once.

I didn't learn all of this in my four weeks of reading with Les, but that was where my education started, as it did for so many of us throughout the decades of conversations with him in offices, during walks along the Charles River, and over lunches at the faculty club. I think just about anyone in the Harvard orbit who trained in psychiatry during the last third of the twentieth century was affected, directly or indirectly, by the view that Leston Havens had of psychiatry, its history, and its potential for the future.

Edward Hundert, MD '84, a psychiatrist, is the HMS dean for medical education and the Daniel D. Federman, M.D. Professor in Residence of Global Health and Social Medicine and Medical Education.

In 2018, the Center for the History of Medicine at the Francis A. Countway Library of Medicine launched the Leston L. Havens MD Teaching Site, part of its Constructing Livable Lives project. The Havens site features his lectures, books, papers, videos, and audios. It is accessible on all digital devices: ***https://www.lestonhavensmd.com/***

DETAILS, UPDATES, AND OBSERVATIONS FROM ALUMNI

How does being a doctor **bring you joy?**

Shirley Driscoll, a pioneer in the fields of perinatal, fetal, and placental pathology and the sixth female professor appointed to HMS, joined some medical students for an outdoor break during orientation day in 1987.

Samuel Kim, MD '62

I find joy in my interactions with patients, parents, students, and other health care personnel.

Richard B. Dobrow, MD '62

I have been retired for nine years, yet I still recall that it was the interactions with patients and seeing their success that brought me the biggest enjoyment.

Joseph McCabe, MD '74

It is a joy to provide assistance to people in need, to see people get better, and to have satisfying professional relationships and intellectual challenges.

Donald Dillon, MD '59

I retired in 1992 after working as a physician for thirty years. A combination of things—the practice of oncology, the 1986 death of my wife from cancer, and a demanding night and weekend call schedule—prevented me from enjoying being a doctor. It all, in fact, led to burnout and some depression.

Carl Needy, MD '49

It brings me joy to help patients get better.

John Merrifield, MD '59

I am retired. My greatest pleasure when seeing patients was listening to their stories, clarifying, occasionally helping. My best job was in a community mental health center.

Lloyd Hamilton, MD '54

Being a physician, taking care of a patient, is still one of the greatest joys of my life. Seeing them feel better and able to live a more enjoyable life ranks with seeing the same in my children. If the patient is grateful, I admit that it adds to the joy, but it is not a necessary ingredient.

Kaihi Fung, MD '82

In general, a physician is able to help people and that should bring joy. In particular, I am a general surgeon. Work that I do tends to bring immediate satisfaction.

"Always admit your mistakes to the patient and his or her family, and apologize for them." That advice has worked for me.

Richard Aadalen, MD '65

The personal gratification that comes from helping patients is tremendous.

William Kupsky, MD '78

As a neuropathologist, my greatest joy is solving diagnostic problems and interacting with neurology and neurosurgery residents as we explore the brain together.

Carolyn Aldredge, MD '63

My continued interaction with patients, their concerns and joys, brings me joy.

Bruce Barnett, MD '75

I am happiest when I am able to help another person.

Howard Rubenstein, MD '57

I am now 87 years old, and long retired, so I have to remember how being a physician brought me joy.

Actually, it is easy to remember.

Joy: A rotating internship at the Los Angeles County General Hospital. Rotating internships are now extinct. I think that's unfortunate. How can a young physician make a good choice of residency without sampling during internship nearly everything medicine has to offer?

Joy: Doing research in the Department of Bacteriology and Immunology at HMS in the laboratory of **Albert Coons**, MD '37. Searching for endotoxin with fluorescent antibodies brought both scientific and aesthetic satisfaction.

Sorrow: Not becoming another Paul Ehrlich.

Joy: Learning as an apprentice to John Harter (I think I may be the last apprenticed physician in the United States).

Joy: Appointed chief of allergy and physician to the Harvard University Health Services and not having a single asthmatic death, nor a single lawsuit, during my many years in practice there. **John Brooks**, MD '43, the famous surgeon, taught me how to avoid lawsuits: "Always admit your mistakes to the patient and his or her family, and apologize for them. Never be defensive or attempt a cover-up." That advice has worked for me.

Joy: To be invited in 1984 as a member of the first group of allergists and clinical immunologists to visit the People's Republic of China, to lecture—and learn—Chinese medicine, and to tour China.

Joy: Spending a summer as an internist at the Albert Schweitzer Hospital in Deschapelles, Haiti. I learned tropical medicine and got to treat the three major illnesses in Haiti: malnutrition, tuberculosis, and neonatal tetanus. Papa Doc had already wiped out yaws with compulsory penicillin.

Sorrow: I developed tinnitus, dysequilibrium, and deafness. My family and I had to leave the snow and ice of Massachusetts and move to a warm climate. I did not wish

to give up practicing some form of medicine, so I searched for a job reading medical records in California and, in 1989, ended up in San Diego doing disability evaluations under Social Security.

Joy: Disability under Social Security is a legal program, and I learned some law, which I enjoyed, and I discovered, to my delight, and contrary to popular belief, that most people applying for disability are honest.

Joy: The privilege of being a physician and of having an interesting and varied career as one. There were opportunities for making good fits between my work and me along the way, and I was rarely troubled by an interfering management. I can't help wondering if not having such opportunities and not having good fits contribute to burnout.

John A. Stanley, MD '58

It's the people that bring me joy—both the patients and the students.

Joseph Burnett, MD '58

I was a professor, so I enjoyed my residents and students. All my papers and books allowed me 153 trips abroad and an appointment as a visiting professor of zoology at the University of Queensland in Brisbane, Australia.

Mary Flowers, MD '78

I was a joyful physician in my remote past. Now the role as a provider sucks—no joy, no challenges, no excitement, no connection to "clients," formerly known as patients.

George Ryan Jr., MD '53

The pleasure of serving patients and earning their trust and respect bring me joy. I also have an MPH from Harvard and have worked as full-time faculty on public health issues and enjoyed some success.

Roy C.A. (Chris) Weatherley-White, MD '58

I have found joy when operating on infants, here and abroad, who have cleft lip and palate anomalies. Receiving the gratitude of parents and knowing you've made a profound difference in a human's life is satisfaction enough.

Sylvester (Skip) Sviokla III, MD '72

In 1999, I lost nearly everything to opioid and alcohol addiction. Fortunately, I didn't lose my family. Working to regain my health and dignity has allowed me a second run at healing by using my experience and newly acquired knowledge in addiction medicine to help others. Being an HMS-trained physician has brought me joy and has provided me opportunities that I have grabbed with gusto, as detailed in my memoir, *From Harvard to Hell . . . and Back*. I'll be working until I reach room temperature.

Brandon Lujan, MD '02

Partnering with patients to understand what is happening to their retina and how treatment is affecting the outcome is tremendously gratifying. Even if I cannot improve someone's vision, I find that when they understand their disease and the rationale for treatment, they are able to accept their disease and move forward with their lives despite their limitations.

Joseph Barr, MD '60

Being respected by patients and friends brings me joy. So does rebuilding patients with new knees and hips to improve their quality of life.

Hugh Hermann, MD '54

My mission is "paying it forward" to the Woodstock, New Hampshire, community and to Dartmouth Medical School for their support of primary care medicine for more than sixty years. This brings me so much joy and is why I still teach and practice.

Ernest Bergel, MD '56

Being a doctor gives me a sense of purpose in life, which is not so easy to achieve at my age. I greatly enjoy my contacts with my psychiatric outpatients, in part because I am exclusively in private practice and not exposed to institutional or financial pressures.

Richard Hirschhorn, MD '58

It brings me joy to feel I possess skills unavailable to others.

Samuel L. Katz, MD '52

I find joy in helping others.

Nathan Selden, MD '93

I enjoy caring for patients, performing surgical procedures, and seeing the benefit when patients return to clinic. Some of my patients still send me annual messages twenty years after the episode of care I was involved in. I enjoy teaching young people, witnessing their enthusiasm, and seeing their maturity and experience grow.

Victor Connell, MD '74

Given that I started practicing medicine when physicians were more autonomous and there was more time spent in patient interaction than in documentation, there has not been much joy in the latter part of my medical career.

The joyful part of practicing medicine is that it can be a lifelong journey that is intellectually stimulating and constantly changing and that it can allow you the opportunity to interact with and assist other people in a meaningful and special way.

Tamara Fountain, MD '88

I enjoy listening to people's stories. I feel honored to witness the tenderness in the way an adult child ministers to a frail parent in the exam room. I feel needed when I can bring some level of reassurance and comfort to a patient who is frightened and overwhelmed—even if I can't fix their problem. And what about the gratitude of our patients? I've saved every card and note a patient has ever written me. If I ever need reassurance or comfort, those notes will remind me that I made a difference.

It feels good to give the gift of improved health to a person. Their gratitude and appreciation (and we don't always get a warm-fuzzy validation of our efforts!) are like an elixir, a drug. It's also a remarkable opportunity to interface with people from all walks of life who've worn different shoes on their life's journey than I have. It's too easy to retreat into one's protected domain with friends and family who share your views. Patients do a good job of taking us out of these comfort zones.

The brilliance, enthusiasm, creativity, optimism, and commitment of this next generation of physicians and scientists is inspiring and keeps me going on long days.

Elizabeth Henske, MD '85

The mentoring of students, postdoctoral fellows, and clinical fellows is a continued source of joy in my career. The brilliance, enthusiasm, creativity, optimism, and commitment of this next generation of physicians and scientists is inspiring and keeps me going on long days.

Marshall Ruffin Jr., MD '78

My joy comes from using my understanding of physiology, pathophysiology, and medicine to help people live healthier and happier lives. Twice in my life, I was nearly killed, first at age 13 in a mountain climbing accident and then a car accident at age 15. Both times, medical treatment kept me alive and allowed me to recover. I grew up wanting to know how to practice medicine and how to help others with a knowledge of medicine. My focus now is on precision medicine and predictive analytics.

Stephen Friedland, MD '57

I retired from pediatric practice sixteen years ago, but I still run into former patients and parents of former patients who, I feel, are genuinely glad to see me and share experiences of their lives since I last treated them. I feel that my time in practice was well spent.

John Welch, MD '68

It is such a joy to unexpectedly meet a person who says something like "You saved my life" or "You operated on me for such and such an illness, and I have done well since." As a retired surgeon who once dealt with a number of patients with acute surgical conditions, I felt joy and satisfaction in those moments for a job well done.

Rita Charon, MD '78

I closed my practice after thirty-four years as a general internist. During that early July when I no longer had a clinic, I felt relief. Someone else was worrying about Lucy. And then, quietly, came the loss of the opportunities for kindness, helping an old woman on with her socks, calling a family member without being asked, planting the PPD skin test myself. More real than empathy, kindness is unnecessary, uncounted, and mutually nourishing. Being physicians gives us the joy of an overflowing account.

William (Jay) Ericson, MD '83

I find joy in being required—and able—to conjure up all of the knowledge I have obtained in training and in practice and apply it to a patient with a long, complicated medical history and multiple vague complaints who is in dire need of a real diagnosis and a rational treatment plan that will reliably relieve their symptoms. Being able to do this on a daily basis is a career filled with joy.

David Fogelson, MD '77

I am an expert psychopharmacologist, but prescribing medication is not what brings me joy. Joy comes to me when I listen to my patients' stories and validate their life experience. I tell every patient that, just as their fingerprint is unique, so is their brain and their story. Because genomics is not yet able to inform what their unique treatment should be, the art of medicine has to come up with the medication cocktail that restores them to full function. Joy comes when it does!

Richard Peinert, MD '73

This answer is short and easy. There are not many professions that allow you to ask at the end of the day, "Did I make something or someone better," and to usually be able to answer, "Yes."

Samyukta Mullangi, MD '15

Being a physician means that I never have a boring work day. I find that every patient I meet is interesting and complex in his or her own way. During my nonclinical time, I ponder what the future of health care will look like, or, more precisely, how technology will revolutionize care processes and pathways. Having that balance between the immediacy of patient care and the long-term outlook of research makes the job fascinating.

Gordon Bae, MD '16

It's a joy to see the dramatic improvement in a patient's quality of life when a disease is well controlled and to reassure patients by providing them with a clear plan of action and then see the amount of stress and fear they had decrease or disappear. The gratitude patients express for the work that I do brings me joy. So does working alongside and developing meaningful relationships with fantastic people who make going to work fun (co-residents, faculty, nurses, and others in medicine).

Thank you to everyone who offered thoughts on how medicine brings them joy.

The next issue of Harvard Medicine *will feature your responses to the question:* ***What were your thoughts when you received your white coat?***

Responses can be submitted online: https://hms.harvard.edu/rounds; via email: hmsalum@hms.harvard.edu; or by mail: Rounds, Alumni Affairs and Development, Harvard Medical School, 401 Park Drive, Boston, MA 02115.

The views expressed in these notes are solely those of the authors and not necessarily those of HMS and Harvard University.

Obituaries

1930s

1938

Burness E. Moore, MD
November 27, 2018

1940s

1943

William R. Eyler, MD
December 5, 2018

1945

Chester Solez, MD
January 30, 2019

1948

Richard W. Nicholson, MD
February 8, 2019

1950s

1950

Robert Bower, MD
March 4, 2019

Leon R. Briggs Jr., MD
January 2, 2019

1953

Philip J. Snodgrass, MD
December 16, 2018

1954

C. Peter Crowe Jr., MD
January 8, 2019

1955

Virginia Gossard Mannick, PhD
February 5, 2019

1956

Thomas K. Hunt, MD
February 20, 2019

George L. Tucker, MD
February 27, 2019

Charles W. Young, MD
December 31, 2018

1960s

1961

Muriel M. Sugarman, MD
February 6, 2019

1963

John Mendelsohn, MD
January 7, 2019

David Savitz, MD
February 13, 2019

1964

Christopher H. Fung, MD
December 5, 2018

1967

John G. Gunderson, MD
January 11, 2019

1970s

1970

Donald Gerson, MD
June 12, 2018

1971

Bruce M. Smith, MD
January 5, 2019

1973

David K. Lee, MD
December 16, 2018

R. Kent Sargent, MD
March 4, 2019

1977

Richard Payne, MD
January 3, 2019

1979

Carolyn S. Spiro, MD
February 17, 2019

1980s

1981

David J. Bryan, MD
December 22, 2018

1987

Giles R. Locke III, MD
January 10, 2019

Judith Pinsker, MD
December 23, 2018

This listing of deceased alumni includes those alumni whose notices of death were received between December 1, 2018, and March 15, 2019.

PRESIDENT'S REPORT

A **Passel of News** for Spring

IN LATE FEBRUARY, the Alumni Council convened its spring meeting in Gordon Hall. Dean George Q. Daley, MD '91, kicked off the day by sharing news of the recent gift from Len Blavatnik and the Blavatnik Family Foundation. The gift will support a therapeutics initiative, spark fertile intellectual communities, encourage collaboration across disciplines, and launch the Blavatnik Harvard Life Lab Longwood. In recognition of this landmark gift, the School established the Blavatnik Institute at HMS. In addition, the dean shared news of recent events, including the first HMS Alumni in Industry Summit, which focused on alumni whose professional paths have taken them to leadership positions in the health care industry sector.

Dean Daley also addressed the pressing issue of MD student financial aid. He announced a $1.2 million increase in annual funding to support a new approach to financial aid that would not only guarantee that full-need students receive full scholarship funding to cover tuition and mandatory fees for four years, but also reduce student debt by $16,000 on average for both new and returning students. HMS continues to maintain a need-based scholarship funding program consistently ranked among the top five in the nation, with 75 percent of our students receiving some type of aid. The Council, including president-elect Michael Rosenblatt, MD '73, plans to continue the close partnership between the Council and the School on this critical topic.

As announced previously in *Harvard Medicine*, we launched a new HMS alumni award: the Distinguished Service Award. Dea Angiolillo, MD '79, is the inaugural recipient. Dea, who will be celebrated at the HMAA annual business meeting on June 7, created and manages the MD Alumni Adviser program, which is highly used by students seeking advice and mentorship from alumni. Dea has demonstrated a quiet and dedicated volunteer commitment that makes an enormous difference to the School, its students, and its alumni.

At the June meeting I will also share news of the individual selected to succeed Tamara Fountain, MD '88, as chair of alumni giving. Tamara has been a wonderful champion of the School, and we are grateful for her service.

Please stay engaged by voting in the Alumni Council elections, sharing your voice in "Rounds," and returning to campus for Reunion and/or Alumni Day. Your participation is critical to our alumni community and our current and future students.

Elizabeth (Lisa) Petri Henske, MD '85, is an HMS professor of medicine at Brigham and Women's Hospital, director of the Center for LAM Research and Clinical Care at Brigham and Women's, director of the Brigham Research Institute, associate member of the Broad Institute of MIT and Harvard, and a medical oncologist at the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute.

Alumni Announcements

Cast your vote in the Alumni Council election

The Harvard Medical Alumni Association Nominating Committee has assembled an outstanding slate of candidates for the Alumni Council. Before casting your vote online, view candidate profiles and personal statements at **alumni.hms.harvard.edu/election**. Votes must be received by noon ET on June 3.

Distinguished Service Award for HMS alumni

The inaugural winner of this award, Dea Angiolillo, MD '79, will be celebrated during the Harvard Medical Alumni Association's annual business meeting on June 7. The award was established this year to recognize individuals who have demonstrated loyalty, service, and commitment to HMS.

Join us for Reunion, June 6-8

Alumni from classes ending in 4 or 9 and their guests are invited to rediscover the campus and rekindle friendships during the 2019 festivities, which will include a gala, faculty and alumni symposia, class-specific events, a family picnic with a cookout and games, and more. Visit **alumni.hms.harvard.edu/reunion** for details and to register.

Alumni Day, June 7

All alumni are invited to attend Alumni Day events, including the dean's State of the School address, the Harvard Medical Alumni Association's annual business meeting, the Alumni Day symposium, and campus tours. Additionally, members of the Society of the Silver Stethoscope—alumni who have celebrated their 60th reunion—are invited to a private lunch. Visit **alumni.hms.harvard.edu/alumni-day** for details and to register.

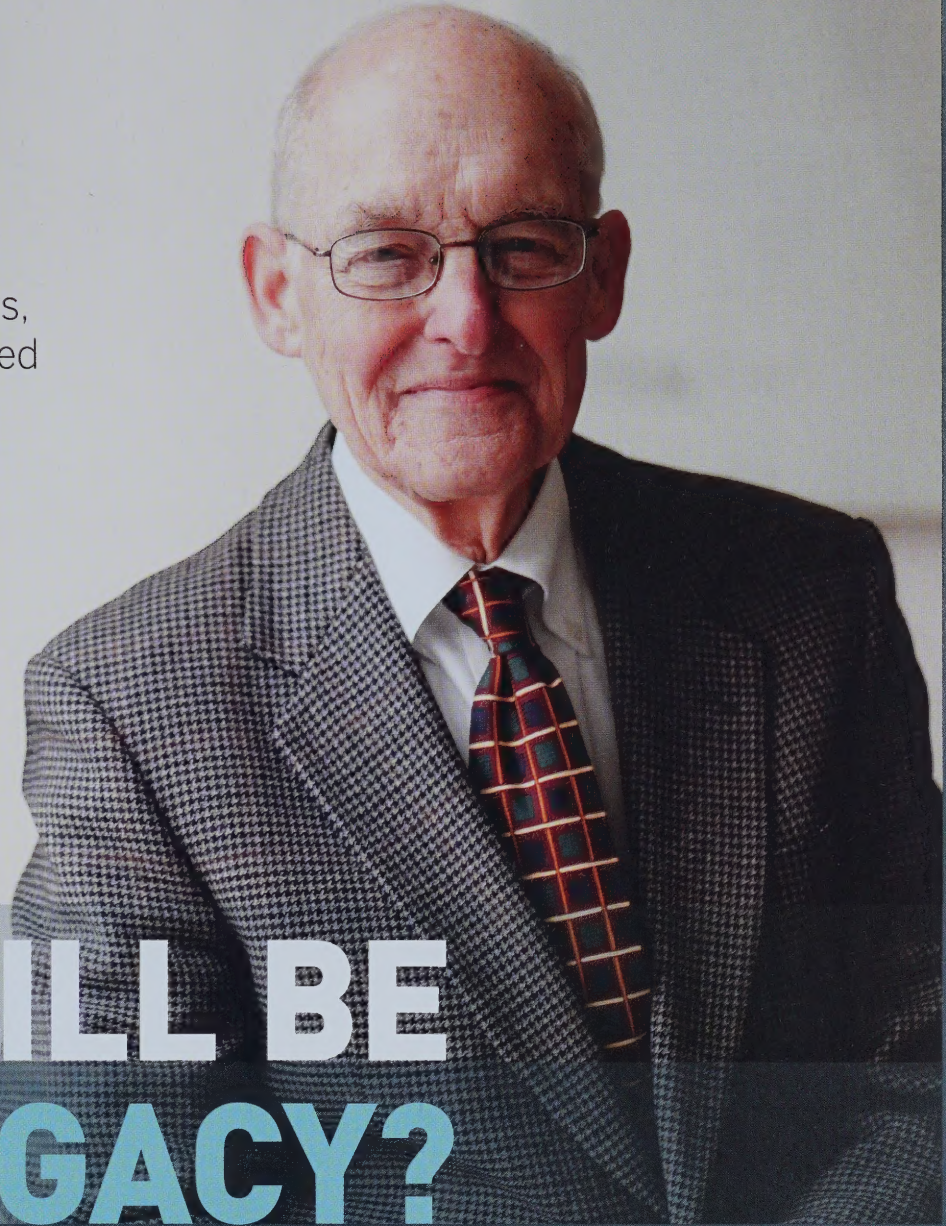
Recent Graduate Gathering, June 8

Mingle with fellow recent HMS grads and enjoy Boston nightlife at the Rooftop@Revere at the Revere Hotel Boston Common. All alumni who graduated in 2004 or later are welcome. For more information, alumni celebrating their 5th, 10th, or 15th reunion should visit **alumni.hms.harvard.edu/reunion** and select their class page. Other alumni should visit **alumni.hms.harvard.edu/recent-grad-gathering**.

HARVARD
MEDICAL SCHOOL

"Harvard Medical School gave me the freedom to explore my interests, leading to experiences that launched my clinical and academic career. I think it's important to give back to the School in some measure what we have been fortunate enough to receive."

—Gordon Moore, AB '59, MD '63, MPH '70
Professor of Population Medicine



WHAT WILL BE YOUR LEGACY?

Gordon Moore has worn several leadership hats over the span of his 55-year career in health care research, design, management, and education. He recently added donor to his list of titles, having named HMS as a beneficiary of his will to support the Department of Population Medicine, where he has worked the last 23 years.

JOIN HIM IN LEAVING A LEGACY AT HMS.

A GIFT TO HMS THROUGH YOUR WILL OR TRUST IS ONE OF THE SIMPLEST WAYS TO LEAVE A LEGACY.

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hms.harvard.edu/bequest

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Samuel Sanker or Kathleen K. Murphy
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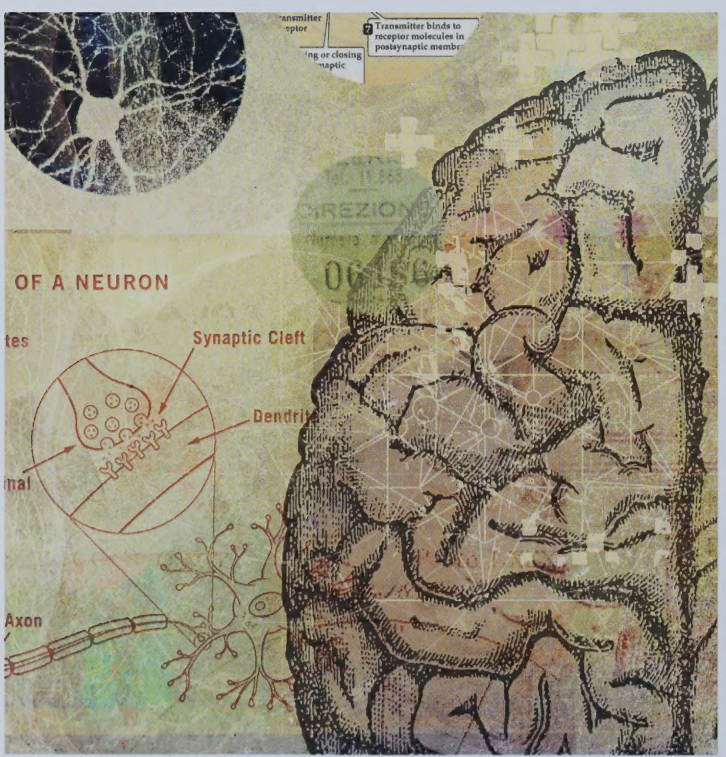

A Deep Look

Unmasking the biological contributors to mental illness could improve the classification, diagnosis, prognosis, screening, and treatment of these disorders and open the door to prevention and treatment that would benefit hundreds of millions globally.